# *AHRQ Systematic Review Surveillance Program*

**CER #21:** Comparative Effectiveness of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications vs Usual Care

**Original Release Date:** May 2010
**Surveillance Report:** February 2012
**Surveillance Report:** August 2016

## Summary of Key Findings from Surveillance Report:

- **Key Question 1:** Conclusions are likely current.
- **Key Question 2:** Conclusions are likely current.
- **Key Question 3a:** Conclusions are likely current.
- **Key Question 3b:** Conclusions are likely current.
- **Key Question 4a:** Conclusions are likely current.
- **Key Question 4b.i:** Conclusions are likely current.
- **Key Question 4b.ii:** Conclusions are likely current.
- **Key Question 4c:** Conclusions are likely current. One expert noted prostatectomy is now associated with lower morbidity due to the use of laparoscopic and robotic technology, which, although unrelated to conclusions on the off-label use of rFVIIa, provides important context of how the morbidity associated with this surgical procedure has changed over time.

**Signal Assessment:** The signal for this report is **weak** suggesting that the conclusions in the original systematic review **are up to date.**

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## Conflict of Interest:
None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.


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# Introduction

The purpose of the surveillance process for the EPC Program is to determine whether the conclusions of a systematic review are current. The surveillance process examines the conclusions to the key questions as written, and does not evaluate the currency of the original scope (i.e., key questions, included interventions). Approximately 25 systematic reviews are selected for surveillance annually based on popularity, use in obtaining continuing medical education certificates, potential impact for changing the field, and use in clinical practice guidelines.

Comparative Effectiveness Review (CER) #21 titled *Comparative Effectiveness of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications vs Usual Care,* was originally released in May 2010.[1]

The key questions for the original systematic review are as follows:

**Key Question 1.** Indications, Populations, and Characteristics of Comparative Studies of Off-Label rFVIIa Use?

**Key Question 2.** Use of rFVIIa for Selected Indications in Individuals With/Undergoing Intracranial Hemorrhage

**Key Question 3a.** Use of rFVIIa for Selected Indications in Individuals With/Undergoing Massive Bleeding from Trauma (Body Trauma)

**Key Question 3b.** Use of rFVIIa for Selected Indications in Individuals With/Undergoing Massive Bleeding from Trauma (Brain Trauma) i.e., Traumatic Brain Injury [TBI])

**Key Question 4a.** Use of rFVIIa for Selected Indications in Individuals With/Undergoing Liver Transplantation

**Key Question 4b.i.** Use of rFVIIa for Selected Indications in Individuals With/Undergoing Cardiac Surgery (Adult Cardiac Surgery)

**Key Question 4b.ii.** Use of rFVIIa for Selected Indications in Patient With/Undergoing Cardiac Surgery (Pediatric Cardiac Surgery)

**Key Question 4c**. Use of rFVIIa for Selected Indications in Patient With/Undergoing Prostatectomy

Our surveillance assessment began in December 2015. We conducted an electronic search for literature published since the end date of the most recent surveillance report search date. After completing a scan of this literature to identify evidence potentially related to the key questions in this systematic review, we contacted experts involved in the original systematic review to request their opinions as to whether the conclusions had changed.

# Methods

### Prior Surveillance

A surveillance report for the original systematic review was released in February 2012, and included a search for relevant literature published from 2008-Jan 2012 among five general medical journals (Annals of Internal Medicine, BMJ, JAMA, Lancet, and New England Journal of Medicine) and five specialty journals (Journal of Trauma Injury, Infection and Critical Care; NeurocriticalCare; Annals of Thoracic Surgery; Transplantation; and Stroke), expert opinion, and a search of U.S. Food and Drug Administration (FDA) surveillance alerts received from the Emergency Care Research Institute (ECRI). The findings from this report are included in our assessment.

## Literature Searches

We conducted a literature search of Ovid MEDLINE covering January 2012 to December 2015 using the identical search strategy used for the original review[1] and searching for studies published since the end date of the most recent surveillance search.

The literature search to assess the currency of conclusions was conducted among a selection of the top 10 high profile general medical interest journals and specialty journals searched in 2012 surveillance report (Annals of Internal Medicine; Annals of Thoracic Surgery; BMJ; JAMA, Journal of Trauma Injury, Infection and Critical Care; Lancet; Neurocritical Care; New England Journal of Medicine; Stroke; Transplantation). However, because the search yielded fewer than 10 studies, we removed the journal limitations. The search strategy is reported in Appendix A.

## Study Selection

We used the same inclusion and exclusion criteria as the original systematic review, with one exception. The original review included an evaluation of the Premier database from 2000-2008 to "document the complete range of clinical indications where rFVIIa is being used off-label, including information on real-world in-hospital practice patterns" (p. 9).[1] In lieu of conducting an updated analysis of the Premier database, we expanded the inclusion criteria for the first component of KQ1- describing clinical indications of off-label rFVIIa use- to include non-comparative registry studies (see Appendix B for a full description of the inclusion/exclusion criteria).

One investigator reviewed the titles and abstracts of 200 randomly selected articles out of 612 total unique articles identified in the PubMed search (Appendix C). We included systematic reviews and meta-analyses, whether or not they were included (as a study design) in the original systematic review. For systematic reviews and meta-analyses, we considered findings only if all included studies met criteria that a) all studies were not included or excluded from the original systematic review, b) all studies were not included in a prior surveillance report (if applicable), and c) all studies met inclusion criteria for the original systematic review. Reviews for which one or more study did not meet our criteria were used to identify potentially relevant primary research. Reviews of systematic reviews were not included.

## Expert Opinion

We shared the conclusions of the original systematic review and most recent surveillance assessment, findings from the literature analysis, and the newly identified studies with 11 experts in the field (8 original peer reviewers and 3 technical expert panel [TEP] members) to request their assessment of the currency of the original review conclusions and their recommendations of any relevant new studies. Two subject matter experts responded to our

request. See Appendix D for the form experts were asked to complete. Of note, one registry study[2] was not included in the form, as we decided to include registry studies for Key Question 1 after submitting information to experts.

## FDA, Health Canada, and MHRA Warnings

We reviewed results from a search of FDA MedWatch black box warnings, Health Canada surveillance warnings, and Medicines and Healthcare Products Regulatory Agency (MHRA) surveillance warnings. The search was conducted by the Emergency Care Research Institute (ECRI).

## Check for Qualitative Signals

The authors of the original systematic review conducted qualitative and quantitative synthesis of data on indications, populations, and characteristics of comparative studies of off-label rFVIIa use (KQ1), as well as the use of rVIIa among individuals with intracranial hemorrhage (KQ2), body trauma (KQ3a), or traumatic brain injury (KQ3b), or individuals undergoing liver transplantation (KQ4a), adult cardiac surgery (KQ4b.i), pediatric cardiac surgery (KQ4b.ii), or prostatectomy (KQ4c). We compared the conclusions of the included abstracts to the conclusions of the original systematic review and 2012 surveillance report, assessed expert input, and reviewed FDA, Health Canada, and MHRA alert information to identify qualitative signals about the currency of conclusions.

## Compilation of Findings and Conclusions

For this assessment we constructed a summary table (Appendix E) that includes the key questions and conclusions from the original systematic review, findings of the new literature search, and expert assessments pertaining to each key question. Because we did not find any FDA, Health Canada, or MHRA warnings, we did not include a column for this in the summary table. We categorized the currency of conclusions using a 3-category scheme:

- Original conclusion is still valid and this portion of the systematic review is likely current
- Original conclusion is possibly out of date and this portion of the systematic review may not be current
- Original conclusion is out of date.

We considered the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the systematic review conclusion as still valid, we classified the systematic review conclusion as likely current.
- If we found some new evidence that might change the systematic review conclusion, and/or a minority of responding experts assessed the systematic review conclusion as having new evidence that might change the conclusion, then we classified the systematic review conclusion may not be current.
- If we found new evidence that rendered the systematic review conclusion out of date or no longer applicable, we classified the systematic review conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a

black box warning from FDA, etc.

### Signal Assessment for Currency of the Systematic Review

We used the following considerations in our assessment of currency of the systematic review:

- **Strong signal:** A report is considered to have a strong signal if new evidence is identified that clearly renders conclusions from the original systematic review out of date, such as the addition or removal of a drug or device from the market or a new FDA boxed warning.
- **Medium signal:** A report is considered to have a medium signal when new evidence is identified which may change the conclusions from the original systematic review. This may occur when abstract review and expert assessment indicates that some conclusions from the original systematic review may not be current, or when it is unclear from abstract review how new evidence may impact the findings from the original systematic review.
- **Weak signal:** A report is considered to have a weak signal if no new evidence is identified that would change the conclusions from the original systematic review. This may occur when no new evidence is identified, or when some new evidence is identified but it is clear from abstract review and expert assessment that the new evidence is unlikely to change the conclusions of the original systematic review.

## Results

### Prior Surveillance

Prior surveillance of the topic included 15 studies and consultation with two subject matter experts.

- **Key Question 1:** The populations, characteristics and indications of the identified comparative studies[3-12,18-23] were similar to the studies in the original systematic review. Conclusions were determined to not be applicable for the purpose of assessing currency.
- **Key Question 2:** The conclusion of increased risk of arterial TEs with high and medium doses of rFVIIa use for intracranial hemorrhage was determined to be possibly out of date due to a meta-analysis[3] indicating no difference between rFVIIa and no-rFVIIa groups in risk of arterial TEs. *However, it is our assessment that the original conclusion is likely current, because the four relevant studies from the identified meta-analysis[3] had previously been included in the original systematic review.* Two additional RCTs[4,5] were also congruent with the original conclusions on arterial TEs. All other conclusions were determined to be likely current.
- **Key Question 3a:** The conclusion of no difference in mortality between rFVIIa and no-rFVIIa in RCTs and slightly decreased risk of mortality with rFVIIa in observational studies for body trauma were determined to be possibly out of date due to a RCT[6] indicating higher mortality with the use of rFVIIa in a regression analysis, and an observational study[7] indicating lower 24-hour mortality in rFVIIa vs no rFVIIa use among individuals receiving ≥ 30 units of packed red blood cells (RBCs). *However, it is our assessment that the original conclusion is likely current, as the RCT[6] that conducted the regression analysis found similar mortality rates when comparing rFVIIa to no-rFVIIa groups, two other identified RCTs[8,9] were congruent with the findings from the RCTs in the original systematic review, and the identified observational study[7] was congruent*

*with the findings from the observational studies in the original systematic review.* Identified studies were also congruent with the original conclusions on the risk of TEs and units of RBCs transfused.[6,7,9] All other conclusions were determined to be likely current.

- **Key Question 3b:** The conclusion of no evidence on RBC transfusion requirements in rFVIIa groups for traumatic brain injury was determined to be possibly out of date due to an observational study[10] indicating reduced RBC transfusion requirements in the rFVIIa group compared to no-rFVIIa group. *However, it is our assessment that this conclusion is likely current, as evidence remains insufficient to form a conclusion.* Identified studies were congruent with the original conclusions on mortality[10] and arterial TEs.[3,10] All other conclusions were determined to be likely current.
- **Key Question 4a:** The conclusion that there is a trend towards reduced RBC transfusion requirements with rFVIIa use for liver transplantation was determined to be possibly out of date due to a meta-analysis[11] indicating no significant difference between rFVIIa and no-rFVIIa groups. *However, it is our assessment that the original conclusion is likely current, because the studies included in the identified meta-analysis had previously been included in the original systematic review.* This meta-analysis[11] was congruent with the original conclusions for mortality. All other conclusions were determined to be likely current.
- **Key Question 4bi:** Conclusions were determined to be likely current. Findings from one meta-analysis[3] were congruent with the original conclusions of no difference between rFVIIa and no rFVIIa on TEs for adult cardiac surgery. In addition, one observational study[12] that reported conclusions, but no data, on operating room time provided evidence where there was previously none. However, evidence remains insufficient to form a conclusion.
- **Key Question 4bii:** Conclusions were determined to be likely current. Findings from one observational study added to the evidence base on mortality, TEs, and units of whole blood/RBC transfusions for pediatric cardiac surgery, however evidence remains insufficient to form conclusions.
- **Key Question 4c:** Conclusions were determined to be likely current. No new studies were identified on prostatectomy.

## Literature Search

The literature search identified 612 unique titles from the PubMed search. We examined a random selection of 200 of the 612 articles (see Appendix C). Upon abstract review, 153 of the randomly selected studies were rejected because they did not meet the original systematic review inclusion criteria (see Appendix B). The remaining 7 studies[2,5,13-17] were examined for potential to change the results of the original systematic review.

## FDA, Health Canada, and MHRA Black Box Warnings

We did not find any FDA black box warnings, Health Canada surveillance warnings, or MHRA surveillance warnings relevant to the key questions in this systematic review.

## Expert Opinion

We shared the conclusions of the original review with 11 experts in the field (8 original peer reviewers and 3 TEP members) to request their assessment of the currency of report

conclusions and their recommendations of any relevant new studies. Two subject matter experts responded.

One expert felt KQ 2-4c conclusions were up to date, while the other expert did not comment on the currency of conclusions. One expert was surprised we identified no studies on the use of rFVIIa in obstetric populations; however the original systematic review included three retrospective comparative studies on rFVIIa use in obstetrics/gynecology for KQ 1 (note: these studies were not explicitly described on the expert form. The form listed the indications that comprised 69% of the identified comparative studies, ie, cardiac surgery, trauma, intracranial hemorrhage, liver transplantation, and prostatectomy). This expert also noted that prostatectomy is now associated with lower morbidity, given the use of laparoscopic and robotic technology. The other expert identified a relevant study for KQ 1[2]. This expert also identified a potentially relevant study[18] for KQ1, however we excluded it because it examined human rather than recombinant rFVIIa.

## Identifying Qualitative Signals

Appendix E shows the original key questions, the conclusions of the original systematic review and the most recent surveillance report, the results of the literature search, expert opinion, and the assessment of the currency of the systematic review.

- **Key Question 1:** Conclusions are likely current. The 2012 surveillance report noted the populations, characteristics, and indications of identified studies, which were similar to the original review, but did not assess the currency of conclusions. For the 2016 surveillance report, the populations and characteristics of the identified studies were similar to the studies identified in the original systematic review.
- **Key Question 2:** Conclusions are likely current. The 2012 surveillance report determined that the conclusion of increased risk of arterial thromboembolic events (TEs) with high and medium doses of rFVIIa for intracranial hemorrhage was possibly out of date, due to evidence from a meta-analysis[3] indicating no difference between rFVIIa and no-rFVIIa on risk of arterial TEs. *However, it is our assessment that the original conclusion is likely current, because the relevant studies from the identified meta-analysis had previously been included in the original systematic review.* Two additional RCTs[4,5] (one from the 2012 surveillance report and one from the 2016 surveillance report) are congruent with the original review's conclusions.
- **Key Question 3a:** Conclusions are likely current. In the 2012 surveillance report, the conclusion of no difference in the risk of mortality between rFVIIa and no-rFVIIa groups for body trauma in RCTs and lower risk of mortality with rFVIIa in observational studies was determined to be possibly out of date, due to one identified RCT[6] indicated higher mortality with the use of rFVIIa in a regression analysis, and one observational study[7] indicated lower 24-hour mortality for rFVIIa versus no rFVIIa among individuals receiving ≥ 30 units of packed red blood cells (RBC). *However, it is our assessment that the original conclusion is likely current, as the RCT[6] that conducted the regression analysis found similar mortality rates when comparing rFVIIa to no-rFVIIa groups, and the observational study[7] was congruent with the findings from observational studies in the original systematic review.* Two other identified RCTs[8,9] were congruent with the findings from RCTs in the original systematic review. Additional studies identified in the 2012 surveillance report were congruent with the original conclusions on the risk of TEs and units of RBCs transfused.[6,7,9] No studies were identified in the 2016 surveillance report.

- **Key Question 3b:** Conclusions are likely current. The conclusion of no evidence on RBC requirements for rFVIIa use for traumatic brain injury was determined to be possibly out of date due to an observational study[18] identified in the 2012 surveillance report that found reduced RBC units among those in the rFVIIa group. *However, it is our assessment that this conclusion is likely current, as evidence remains insufficient to form a conclusion.* In addition, an observational study[15] identified in the 2016 surveillance report found no difference between rFVIIa and no-rFVIIa groups on length of ICU stay where no evidence was found in the original review. Evidence remains insufficient to form a conclusion.
- **Key Question 4a:** Conclusions are likely current. The 2012 surveillance report determined that the conclusion of a trend towards reduced RBC transfusion requirements for liver transplantation with rFVIIa use may be out of date due to a meta-analysis[11] that reported no difference in RBC usage between rFVIIa and no-rFVIIa. *However, it is our assessment that the original conclusion is likely current, because the studies from the meta-analysis had previously been included in the original systematic review.* This meta-analysis[11] was congruent with the original conclusions for mortality. In addition, while the original systematic review only reported on prophylactic use of rFVIIa, the 2016 surveillance report identified one observational study indicating that the intraoperative use of rFVIIa is associated with worse outcomes in mortality, blood product usage, and ICU length of stay compared to prophylactic use or no-rFVIIa. Although this study does not change the currency of the original conclusions, it contributes new evidence comparing timing of rFVIIa administration, which was not reported in the original systematic review.
- **Key Question 4b.i:** Conclusions are likely current. Findings from one meta-analysis[3] were congruent with the original conclusions of no difference between rFVIIa and no rFVIIa on TEs for adult cardiac surgery. In addition, one observational study[12] that reported conclusions, but no data, on operating room time provided evidence where there was previously none. However, evidence remains insufficient to form a conclusion. No studies were identified in the 2016 surveillance report.
- **Key Question 4b.ii:** Conclusions are likely current. No evidence on the use of rFVIIa on mortality in pediatric cardiac surgery was identified in the original systematic review, while the 2012 and 2016 surveillance reports each identified one observational study[8,14] indicating no difference in mortality rates between rFVIIa and no-rFVIIa. Evidence remains insufficient to form a conclusion. Additionally, while there was insufficient evidence on TEs and units of whole blood/RBC transfusions in the original systematic review, the observational studies[8,14] identified in the 2012 and 2016 surveillance reports found no difference between rFVIIa and no-rFVIIa on either outcome. Evidence remains insufficient to form conclusions.
- **Key Question 4c:** Conclusions are likely current. No new studies were identified in either the 2012 or 2016 surveillance reports. One expert noted prostatectomy is now associated with lower morbidity due to the use of laparoscopic and robotic technology, which, although unrelated to conclusions on the off-label use of rFVIIa, provides important context of how morbidity associated with this surgical procedure has changed over time.

## Signal Assessment

The SRC conclusions based on the results of the prior surveillance assessment, literature published since the original report, FDA, Health Canada, and MHRA Warnings, and expert

assessment is that:

- **Key Question 1:** Conclusions are likely current.
- **Key Question 2:** Conclusions are likely current.
- **Key Question 3a:** Conclusions are likely current.
- **Key Question 3b:** Conclusions are likely current.
- **Key Question 4a:** Conclusions are likely current.
- **Key Question 4b.i:** Conclusions are likely current.
- **Key Question 4b.ii:** Conclusions are likely current.
- **Key Question 4c:** Conclusions are likely current. One expert noted prostatectomy is now associated with lower morbidity due to the use of laparoscopic and robotic technology, which, although unrelated to conclusions on the off-label use of rFVIIa, provides important context of how the morbidity associated with this surgical procedure has changed over time.

The signal for this report is **weak** suggesting that the conclusions in the original systematic review **are up to date.**

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# Appendices

**Appendix A: Search Strategy**

**Appendix B: Inclusion and Exclusion Criteria from Original Systematic Review**

**Appendix C: Literature Search Results**

**Appendix D: Questionnaire Sent to Expert Reviewers**

**Appendix E: Summary Table**

# Appendix A. Search Strategy

**Factor VIIa – Main Search**

| | |
|---|---|
| Database Searched December 18, 2015 | Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to November Week 3 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 17, 2015> |
| Original Search Strategy | 1 exp factor viia/ (3637)<br>2 ("factor viia" or "factor 7a" or rfviia or fviia).mp. (5074)<br>3 (novoseven or eptacog* or Niastase or proconvertin or "novo - seven").mp. (596)<br>4 ec 3 4 21 21.rn. (2979)<br>5 (((7a or viia) adj5 (factor or rfactor)) or (("factor vii" or "factor 7" or fvii or rfvii or "factor seven") adj5 (active or activa ted))).mp. (4765)<br>6 1 or 2 or 3 or 4 or 5 (5391)<br>7 ("case reports" or editorial or "review").pt. (4174791)<br>8 animals/ not humans/ (4072764)<br>9 exp Intracranial Hemorrhages/ (60446)<br>10 exp Brain/ (1052784)<br>11 exp Skull/ (171184)<br>12 (intracranial or intracerebral or "basal ganglia" or brain* or "posterior fossa" or cerebral or parenchymal or subdural or subarachnoid or pituitary or epidural).mp. (1666061)<br>13 9 or 10 or 11 or 12 (2053439)<br>14 exp "Wounds and Injuries"/ or (traum* or injur* or wound*).mp. (1461680)<br>15 exp liver transplantation/ (47482)<br>16 ((liver* or hepatic) adj3 (transplan* or graft*)).mp. (62427)<br>17 exp Cardiovascular Diseases/su (267824)<br>18 exp cardiovascular surgical procedures/ (310276)<br>19 ((heart* or ca rdi*) and surg*).mp. (128852)<br>20 exp Prostatectomy/ (25523)<br>21 (Prostatectom* or (resect* and prostat*)).mp. (36766)<br>22 15 or 16 or 17 or 18 or 19 or 20 or 21 (617063)<br>23 6 and (13 or 14 or 22) (1590)<br>24 animals/ not humans/ (4072764)<br>25 23 not 24 (1487)<br>26 6 not (7 or 8 or 25) (2322) |
| Date Limit | 27 limit 26 to yr="2012 -Current" **(368)** |
| Journal Limit | 28 ("annals of internal medicine" or bmj or jama or lancet or "new england journal of medicine").jn. (494798)<br>29 ("annals of thoracic surgery" or "journal of trauma injury infection & critical care" or stroke or transpla ntation or neurocritical care).jn. (66491)<br>30 28 or 29 (561289)<br>31 27 and 30 **(3)** |
| | ***Journal limit yields <10 results, all results from date limit are reviewed(368)*** |

**Factor VIIa - Intracranial Hemorrhage**

| | |
|---|---|
| Database Searched December 18, 2015 | Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to November Week 3 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 17, 2015> |
| Original Search Strategy | 1 exp factor viia/ (3637)<br>2 ("factor viia" or "factor 7a" or rfviia or fviia).mp. (5074) |

| | |
|---|---|
| | 3 (novoseven or eptacog* or Niastase or proconvertin or "novo - seven").mp. (596)<br>4 ec 3 4 21 21.rn. (2979)<br>5 (((7a or viia) adj5 (factor or rfactor)) or (("factor vii" or "factor 7" or fvii or rfvii or "factor seven") adj5 (active or activa ted))).mp. (4765)<br>6 1 or 2 or 3 or 4 or 5 (5391)<br>7 exp Intracranial Hemorrhages/ (60446)<br>8 exp Brain/ (1052784)<br>9 exp Skull/ (171184)<br>10 (intracranial or intracerebral or "basal ganglia" or brain* or "posterior fossa" or cerebral or parenchymal or subdural or subarachnoid or pituitary or epidural).mp. (1666061)<br>11 7 or 8 or 9 or 10 (2053439)<br>12 6 and 11 (501)<br>13 animals/ not humans/ (4072764)<br>14 12 not 13 (485) |
| Date Limit | 15 limit 14 to yr="2012 -Current" (**87**) |
| | ***No journal limits used as results from date limit is <100*** |

**Factor VIIa -Liver Transplantation, etc**

| | |
|---|---|
| Database Searched December 18, 2015 | Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to November Week 3 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 17, 2015> |
| Original Search Strategy | 1 exp factor viia/ (3637)<br>2 ("factor viia" or "factor 7a" or rfviia or fviia).mp. (5074)<br>3 (novoseven or eptacog* or Niastase or proconvertin or "novo - seven").mp. (596)<br>4 ec 3 4 21 21.rn. (2979)<br>5 (((7a or viia) adj5 (factor or rfactor)) or (("factor vii" or "factor 7" or fvii or rfvii or "factor seven") adj5 (active or activa ted))).mp. (4765)<br>6 1 or 2 or 3 or 4 or 5 (5391)<br>7 exp liver transplantation/ (47482)<br>8 ((liver* or hepatic) adj3 (transplan* or graft*)).mp. (62427)<br>9 exp Cardiovascular Diseases/su (267824)<br>10 exp cardiovascular surgical procedures/ (310276)<br>11 ((heart* or cardi*) and surg*).mp. (210008)<br>12 exp Prostatectomy/ (25523)<br>13 (Prostatectom* or (resect* and prostat*)).mp. (36766)<br>14 7 or 8 or 9 or 10 or 11 or 12 or 13 (658165)<br>15 6 and 14 (554)<br>16 animals/ not humans/ (4072764)<br>17 15 not 16 (545) |
| Date Limit | 18 limit 17 to yr="2012 -Current" **(113)** |
| Journal Limit | 19 ("annals of internal medicine" or bmj or jama or lancet or "new england journal of medicine").jn. (494798)<br>20 ("annals of thora cic surgery" or "journal of trauma injury infection & critical care" or stroke or transplantation or neurocritical care).jn. (58094)<br>21 19 or 20 (552892)<br>22 18 and 21 (0) |
| | ***Journal limit yields zero results, all results from date limit are reviewed (113)*** |

**Factor VIIa –Trauma**

| | |
|---|---|
| Database Searched | Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to |

| | |
|---|---|
| December 18, 2015 | November Week 3 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 17, 2015>\ |
| Original Search Strategy | 1 exp factor viia/ (3637)<br>2 ("factor viia" or "factor 7a" or rfviia or fviia).mp. (5074)<br>3 (novoseven or eptacog* or Niastase or proconvertin or "novo - seven").mp. (596)<br>4 ec 3 4 21 21.rn. (2979)<br>5 (((7a or viia) adj5 (factor or rfactor)) or (("factor vii" or "factor 7" or fvii or rfvii or "factor seven") adj5 (active or activa ted))).mp. (4765)<br>6 1 or 2 or 3 or 4 or 5 (5391)<br>7 exp "Wounds and Injuries"/ or (traum* or injur* or wound*).mp. (1461680)<br>8 6 and 7 (916)<br>9 animals/ not humans/ (4072764)<br>10 8 not 9 (828) |
| Date Limit | 11 limit 10 to yr="2012 -Current" **(140)** |
| Journal Limit | 12 ("annals of internal medicine" or bmj or jama or lancet or "new england journal of medicine").jn. (494798)<br>13 ("annals of thoracic surgery" or "journal of trauma injury infection & critical care" or stroke or transplantation or neurocritical care).jn. (89643)<br>14 12 or 13 (584441)<br>15 11 and 14 **(1)** |
| | **Journal limit has <10 results, all results from date limit are reviewed (140)** |

# Appendix B. Inclusion and Exclusion Criteria from Original Systematic Review

Inclusion criteria:
Off-label indications included:

- KQ1: All indications
- KQ2-4: Intracranial hemorrhage, body trauma, traumatic brain injury, liver transplantation, adult cardiac surgery, pediatric cardiac surgery, prostatectomy.

Outcomes included:

- All indications: transfusion requirements, mortality, thromboembolic events
- Intracranial hemorrhage: relative or absolute change in hematoma volume, functional outcome as measured by the modified Rankin Scale (mRS)
- Body trauma: Acute respiratory distress syndrome (ARDS)
- Traumatic brain injury: Relative or absolute change in hematoma volume
- Liver transplantation: Operating room (OR) time, intensive care unit (ICU) length of stay
- Adult cardiac surgery: ICU length of stay
- Pediatric cardiac surgery: Time to chest closure in operating room

Comparators included usual care/standard care.
Study designs:

- Key Question 1: RCTs and comparative observational studies were included. In the original systematic review, authors conducted an examination of Perspective Comparative Database of Premier from 2000-2008 to review trends and the range of clinical conditions in which in-hospital, off-label rFVIIa is used, to examine the clinical and demographic characteristics of cases, and to evaluate the relevance of the indications selected for in-depth effectiveness review. For the 2016 surveillance report, we included registry studies as a means of capturing similar data on indications, populations, and characteristics of off-label rFVIIa.
- Key Question 2-4: RCTs and comparative observational studies were included for the evaluation of effectiveness. Non-comparative observational studies were included for the evaluation of harms.

Exclusion criteria:

- Abstracts only
- Inappropriate intervention or outcome, such as:
- Human FVIIa and modified forms of rFVIIa that are still under development
- Outcomes such as metabolism or half-life that are not clinically relevant
- Studies in healthy volunteers directed at monitoring parameters such as INR or thromboelastin time.
- In vitro studies
- On-label indications of rFVIIa (hemophilia A or B with inhibitors and congenital factor VII deficiency) or those that are substantially similar to on-label indications (Glanzmann's thrombasthenia, hemophilia C, von Willebrand disease, Bernard-Soulier syndrome, Hermansky-Pudlak syndrome, and other congenital bleeding disorders.)

## Appendix C. Literature Search Results

The literature search identified 612 unique titles. Listed below are the 200 randomly selected articles we examined in our assessment of the currency of conclusions in the original systematic review.


1. Abbonizio F, Giampaolo, A., Coppola, A., Italian Association of Haemophilia Centres, Arcieri, R., Hassan, HJ. Therapeutic management and costs of severe haemophilia A patients with inhibitors in Italy. *Haemophilia.* 2014;20(4):e243-250.
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3. Aberg M, Eriksson, O., Siegbahn, A. Tissue Factor Noncoagulant Signaling: Mechanisms and Implications for Cell Migration and Apoptosis. *Seminars in Thrombosis & Hemostasis.* 2015;41(7):691-699.
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## Appendix D. Questionnaire Sent to Expert Reviewers

# *AHRQ Systematic Review Surveillance Program*

**Reviewer Form**

**Title of Original Systematic Review**: Comparative Effectiveness of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications vs. Usual Care
Link to Report

**Most Recent Surveillance Published**: February 2012
Link to Surveillance Report

**Name of Reviewer**: _____

**Instructions:**

The Agency for Healthcare and Research Quality (AHRQ) Scientific Resource Center (SRC) periodically conducts surveillance of published AHRQ systematic reviews to assess the currency of review conclusions. The goal of this process is to identify signals that a report may be out of date. One part of this process includes soliciting expert review of our synthesis of recently published literature and previous surveillance assessments.

The original systematic review was published in May 2010. The original systematic review search dates went through August 2009. Previous surveillance was conducted on February 2012, with the most recent search extending through January 2012. We conducted a bridged literature search of select high impact journals from January 2012 to December 2015 and identified evidence potentially related to the key questions of the original systematic review.

The table below highlights the conclusions from the original systematic review, the findings and assessment of the most recent surveillance assessment, and a summary of the relevant recently published literature. Abstracts from relevant literature are included at the end of the document. If you would like a list of our full search results, please let us know.

Please review the table and provide responses to the questions for each key question below. The primary goal of this review is to identify any important new studies, drugs, interventions, or devices you know of that we may have missed in our literature search and to understand if any new evidence exists which may alter the conclusions of the original systematic review.

Note: When examining the studies identified in the 2012 surveillance assessment, we found that a meta-analysis of 35 randomized controlled trials (RCTs)[3] and a meta-analysis of four RCTs[11] should not have been included, as all relevant studies were included in the original systematic review. The summaries of key questions below describe the impact of removing these studies

on our assessment of currency. In addition, descriptions of the meta-analyses are retained in the attached table (in italics), as a historical record.

## Key Question 1:

Indications, Populations, and Characteristics of Comparative Studies of Off-Label rFVIIa Use?

**Prior Surveillance Assessment (2/2012) and Current Literature Analysis:**

- Indications for off-label recombinant Factor VIIa (rFVIIa) use were consistent in the 2012 surveillance report as in the original systematic review. Studies examined rFVIIa use for intracranial hemorrhage (three studies[3,4,19]), body trauma (eight studies[3,6-10,18,19]), traumatic brain injury (one study[3]), and those undergoing cardiac surgery (two studies[3,12,20]) and liver transplantation.[11]
    - Note: One of the meta-analyses we excluded upon review[11] examined rFVIIa for liver transplantation. This was the only study examining rFVIIa for liver transplantation; thus, no new evidence was identified. The second excluded meta-analysis,[3] included studies examining rFVIIa for intracranial hemorrhage, traumatic brain injury (TBI), body trauma, and adult cardiac surgery.
- Consistent with the original systematic review, the 2012 literature search identified both RCTs,[4,8,9,18,21] and observational studies.[6,7,10,12,19,20,22] One systematic review[23] and *two meta-analyses*[3,11] were also identified, although the meta-analyses were later removed because all relevant studies were included in the original systematic review.
- Consistent with the original systematic review, a wide range of ages (24-76 years old) and dosages of rFVIIa (5-360 µg/kg of patient weight) were represented. The sample size of included studies ranged from 169[18] to *1,397*[3] among RCTs and 24[12] to 2,050[6] in observational studies, which is consistent with the range found in the original review.
    - Note: One of the removed meta-analysis[3] included a study of n=1,397, which was the highest reported sample size identified in the prior surveillance assessment. Exclusion of the meta-analysis lowers the upper range of the sample size of identified studies to n=841. No other changes to the study population or characteristics reported in the prior assessment resulted from the removal these meta-analyses.[3,11]
- Consistent with the original systematic review, most studies reported direct outcomes, such as thromboembolic events[3,4,6,8,10,11,19,20,23] and mortality.[6-8,10,11,18,21,23]

**Current Literature Analysis:**

- In general, we identified indications for off-label rFVIIa use that were consistent with the original systematic review: intracranial hemorrhage (one study[5]), body trauma (one study[13]), traumatic brain injury (two studies[15,17]), liver transplantation (one study[16]), and pediatric cardiac surgery (one study[14]).
- Most of studies included in this surveillance report were observational; only one RCT[5] was identified. Sample sizes ranged from a minimum of n= 21[5] to n=183[16] individuals, which is lower than the sample size found in the original review.
- Consistent with the original review, studies varied in the dosage of rFVIIa administered, and one identified study compared high and low doses.[13]
- Consistent with the original review, most studies reported direct outcomes, such as mortality[14-17,24] and thromboembolic events (TEs).[5,13,14,24]

**Reviewer Questions:**

1. Are the original report conclusions still supported by the current evidence?

| Click here to enter text. |
|---|

2. Are there any published or unpublished studies that you know of that we may have overlooked?

| Click here to enter text. |
|---|

## Key Question 2:

Use of rFVIIa for Selected Indications in Individuals With/Undergoing Intracranial Hemorrhage?

**Prior Surveillance Assessment (02/2012):**

- Conclusions related to arterial thromboembolic events (TEs) are likely out of date due to "lack of evidence" in the original review. The prior surveillance report identified a *meta-analysis*[3] and a RCT[4] *which found that that rFVIIa was associated with higher rates of arterial TEs compared to usual care,*[3] and that high doses of rFVIIa were associated with higher rates of TEs compared to low doses and usual care.[4]
    - It is our assessment that the assessment *should have been* that the original conclusion is likely current. The original review included a meta-analysis of four studies (rated as moderate strength of evidence) that found significantly higher rates of TEs among high and medium doses of rFVIIa compared to usual care but no difference among low doses of rFVIIa compared to usual care (p. 54).
        - The RCT[4] identified in the prior assessment is consistent with the conclusion in the original review.
        - The identified meta-analysis[3] was one of the meta-analyses we excluded due to all studies being included in the original review. Results of the meta-analysis were consistent with the conclusions of the original review; therefore, our exclusion has no impact on the assessment of currency.
- All other conclusions are likely current.

**Current Literature Analysis:**

- We identified a RCT[5] that found similar frequencies of deep venous thrombosis when comparing rFVIIa to placebo, and decreased intracerebral hemorrhage volumes associated with rFVIIa use following hematoma evacuation.

**Reviewer Questions:**

1. Are the original report conclusions still supported by the current evidence?

| Click here to enter text. |
|---|

2. Are there any published or unpublished studies that you know of that we may have overlooked?

| Click here to enter text. |
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## Key Question 3a:

Use of rFVIIa for Selected Indications in Individuals With/Undergoing Massive Bleeding from Trauma?

**Prior Surveillance Assessment (02/2012):**

- Conclusions related to mortality are possibly out of date. The prior surveillance report identified four studies[6-9] examining mortality. Two studies were congruent with the original systematic review's conclusion of no difference between rFVIIa and no-rFVIIa groups,[8,9] one RCT[6] found a higher mortality rate in the rFVIIa group, and one study[7] found that among individuals who received ≥ 30 units of packed red blood cells ( RBCs),

24-hour mortality was lower among those who received rFVIIa compared to those who didn't.

- All other conclusions are likely current. Findings were congruent with the original systematic review's conclusions related to *TEs*[3,8] and RBC requirements.[6,7,9]
    - The identified meta-analysis[3] was one of the meta-analyses we excluded due to all studies being included in the original review. Results of the meta-analysis were consistent with the conclusions of the original review; therefore, our exclusion has no impact on the assessment of currency.

**Current Literature Analysis:**

- We identified one study[13] that found similar rates of TEs among individuals receiving high or low doses of rfVIIa.

**Reviewer Questions:**

1. Are the original report conclusions still supported by the current evidence?

| Click here to enter text. |
|---|

2. Are there any published or unpublished studies that you know of that we may have overlooked?

| Click here to enter text. |
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## Key Question 3b:

Use of rFVIIa for Selected Indications in Individuals with/Undergoing Massive Bleeding from Trauma (Brain Trauma, i.e., Traumatic Brain Injury [TBI])?

**Prior Surveillance Assessment (02/2012):**

- Conclusions related to RBC transfusion are possibly out of date. No studies examining the effect of rFVIIa on RBC transfusion in individuals undergoing massive bleeding from brain trauma were identified in the original systematic review. One identified study[10] examining mortality, TEs, and RBC transfusion requirements found a significant reduction in RBC use in the rFVIIa group, and congruent with the original systematic review, found no difference between groups in TEs or mortality. *An additional meta-analysis[3] also found no difference between groups on arterial TEs.* All other conclusions are likely current.
    - The identified meta-analysis[3] was one of the meta-analyses we excluded due to all studies being included in the original review. Results of the meta-analysis were consistent with the conclusions of the original review; therefore, our exclusion has no impact on the assessment of currency.

**Current Literature Analysis:**

- We identified two studies examining mortality comparing rFVIIa to no-rFVIIa that found no difference between groups.[15,17]
- One study[15] also found no occurrence of TEs in either group and no difference between groups on length of intensive care unit (ICU) stay.

**Reviewer Questions:**

1. Are the original report conclusions still supported by the current evidence?

| Click here to enter text. |
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2. Are there any published or unpublished studies that you know of that we may have overlooked?

| Click here to enter text. |
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## Key Question 4a:

Use of rFVIIa for Selected Indications in Individuals With/Undergoing Liver Transplantation?

**Prior Surveillance Assessment (02/2012):**

- The original review's conclusion of a trend towards reduced RBC transfusion requirements with rFVIIa compared to usual care is possibly out of date. *One meta-analysis[11] was identified, which examined the effect of rFVIIa for RBC transfusions and mortality and found that found no significant difference between groups.*
    - The identified meta-analysis[11] was one of the meta-analyses we excluded due to all studies being included in the original review. Of note, two of the studies from the meta-analysis were included in the original review for liver transplantation, and two were included for other surgery. No other studies examining rFVIIa use on RBC transfusions were identified; therefore, it is our assessment that the prior surveillance should have determined that the conclusions were likely current. Conclusions related to mortality are likely current.
- All other conclusions are likely current.

**Current Literature Analysis:**

- We identified one study[16] that found that individuals receiving rFVIIa before surgery had longer ICU stays compared to usual care. In addition, those who received rFVIIa intraoperatively required more blood products and had higher mortality (30 days and one year) compared to individuals receiving rFVIIa preemptively and those receiving usual care.

**Reviewer Questions:**

1. Are the original report conclusions still supported by the current evidence?

| Click here to enter text. |
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2. Are there any published or unpublished studies that you know of that we may have overlooked?

| Click here to enter text. |
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## Key Question 4b.i:

Use of rFVIIa for Selected Indications in Individuals with/Undergoing Cardiac Surgery (Adult Cardiac Surgery)?

**Prior Surveillance Assessment (02/2012):**

- Conclusions are likely current. The previous surveillance report identified *a meta-analysis examining TEs.*[3] Findings were consistent with the original review and found no difference between groups. In addition, also consistent with the original review, one identified study reported no data on operating room time.[12]
    - The identified meta-analysis[3] was one of the meta-analyses we excluded due to all studies being included in the original review. Results of the meta-analysis were consistent with the conclusions of the original review; therefore, our exclusion has no impact on the assessment of currency.

**Current Literature Analysis:**

- No new studies were identified.

**Reviewer Questions:**

1. Are the original report conclusions still supported by the current evidence?

| Click here to enter text. |
|---|

2. Are there any published or unpublished studies that you know of that we may have overlooked?

| Click here to enter text. |
|---|

## Key Question 4b.ii:

Use of rFVIIa for Selected Indications in Individuals with/Undergoing Cardiac Surgery (Pediatric Cardiac Surgery)?

**Prior Surveillance Assessment (02/2012):**

- Conclusions are likely current. One study,[20] congruent with the original systematic review's conclusions, found no difference between groups in mortality, TEs, and RBCs transfusion requirements.

**Current Literature Analysis:**

- We identified one study[14] that found no significant difference between individuals administered rFVIIa before or after surgery compared to a matched no-rFVIIa group on mortality or rate of thrombosis.

**Reviewer Questions:**

1. Are the original report conclusions still supported by the current evidence?

| Click here to enter text. |
|---|

2. Are there any published or unpublished studies that you know of that we may have overlooked?

| Click here to enter text. |
|---|

## Key Question 4c:

Use of rFVIIa for Selected Indications in Individuals with/Undergoing Prostatectomy?

**Prior Surveillance Assessment (02/2012):**

- Conclusions are likely current. No new studies were identified.

**Current Literature Analysis:**

- No new studies were identified.

**Reviewer Questions:**

1. Are the original report conclusions still supported by the current evidence?

| Click here to enter text. |
|---|

2. Are there any published or unpublished studies that you know of that we may have overlooked?

| Click here to enter text. |
|---|

# Original Systematic Review Conclusions and Literature Analysis

**Title of Original Systematic Review:** Comparative Effectiveness of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications vs. Usual Care

**Original Systematic Review Published:** May 2010
**Original Systematic Review Search Dates:** Key Question 1: 2008-2008 in Premier database; Key Questions 2-4: Database inception-August 2009

**Most Recent Surveillance Report Published:** February 2012
**Most Recent Surveillance Report Search Dates:** January 2008-January 2012

**Current Literature Search Dates:** January 2012-December 2015

The conclusions from the original systematic review, the findings and assessment of the most recent surveillance assessment and a summary of the relevant recently published literature. Abstracts are provided at the end of the document.

Table 1. Key Question 1: Indications, Populations, and Characteristics of Comparative Studies of Off-Label rFVIIa Use?

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) |
|---|---|---|
| **Indications and populations of comparative studies:**<br>Off-label rFVIIa use was examined in 24 RCTs and 31 comparative observational studies across a variety of clinical indications, including cardiac surgery (12 studies), trauma (nine studies), intracranial hemorrhage (ICH) (eight studies), liver transplantation (eight studies), and prostatectomy (one). These studies accounted for 69% of the included off-label rFVIIa studies. There were prominent community uses that lacked studies, such as primary clotting disorders other than hemophilia, secondary clotting disorders, and gastrointestinal bleeding not related to liver disease. Other indications with no studies | **Indications and populations of comparative studies:**<br>Indications for off-label rFVIIa use were consistent in the 2012 surveillance report as in the original systematic review. Studies examined rFVIIa use *for intracranial hemorrhage (three studies[3,4,19]), body trauma (eight studies[3,6-10,18,19]), traumatic brain injury (one study[3]) and those undergoing cardiac surgery (two studies[3,12,20]) and liver transplantation[11].*<br><br>**Characteristics of comparative studies:**<br>Consistent with the original systematic review, the 2012 literature search identified both RCTs[4,8,9,18,21], and observational | **Indications and populations of comparative studies:**<br>In general, we identified indications for off-label rFVIIa use that were consistent with the original systematic review: intracranial hemorrhage (one study[5]), body trauma (one study[13]), traumatic brain injury (two studies[15,17]), liver transplantation (one study[16]), and pediatric cardiac surgery (one study[14]).<br><br>**Characteristics of comparative studies:**<br>Most of studies included in this surveillance report were observational; only one RCT[5] was identified. Sample sizes ranged from a minimum of n= 21[5] to n=183[16] individuals, which is lower than the sample size found in |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) |
|---|---|---|
| included aortic aneurysm, other vascular procedures, and neonatal use (beyond cardiac surgery). Many studies examined only prophylactic use of rFVIIa for clinical indications where treatment or end-stage use may also be frequent. Individuals included in the comparative studies were generally younger and had lower clinical acuity in comparison to individuals in community practice.<br><br>**Characteristics of comparative studies:** With the exception of use in ICH, study sample sizes were small (median of 24 treated individuals). Studies of ICH included two large RCTs of almost 900 individuals treated with rFVIIa. Dosage varied from 5 to 956 mcg/kg of patient weight, and only for intracranial hemorrhage was there a sufficient range of doses to assess the impact of rFVIIa dosing on outcomes. Most studies used indirect endpoints as their primary outcomes, particularly red blood cell (RBC) transfusion requirements, blood loss, and duration of surgery or Intensive Care Unit (ICU) stay. Direct outcomes, such as mortality, functional status, or thromboembolic events, were frequently reported, but most studies were individually underpowered to evaluate them. | studies[6,7,10,12,19,20,22]. One systematic review[23] and *two meta-analyses*[3,11] were also identified. Also consistent with the original systematic review, a wide range of ages (24-76 years old) and dosages of rFVIIa (5-360 µg/kg of patient weight) were represented. The sample size of included studies ranged from 169[18] to *1,397*[3] among RCTs and 24[12] to 2,050[6] in observational studies, which is consistent with the range found in the original review. Also consistent with the original systematic review, most studies reported direct outcomes, such as *thromboembolic events*[3,4,6,8,10,11,19,20,23] *and mortality.*[6-8,10,11,18,21,23] | the original review. Consistent with the original review, studies varied in the dosage of rFVIIa administered, and one identified study compared high and low doses[13]. Consistent with the original review, most studies reported direct outcomes, such as mortality[14-17,24] and thromboembolic events (TEs).[5,13,14,24] |

*Abbreviations:* ICH=Intracranial Hemorrhage; ICU=Intensive Care Unit; RBC=Packed Red Blood Cells; RCT=Randomized Controlled Trial; rFVIIa=Recombinant Factor Seven-A; TE=Thromboembolic Events

*Studies in italics*= the prior surveillance assessment identified two meta-analyses[3,11]; however upon further review, we discovered that all studies included in these meta-analysis, for these indications, appeared in the original systematic review. Thus, we are not considering these meta-analyses in the determination of currency.

Table 2. Key Question 2: Use of rFVIIa for Selected Indications in Individuals With/Undergoing Intracranial Hemorrhage

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) |
|---|---|---|
| **Outcome: Mortality (90 day)**<br>**SOE: Moderate**<br>**Four RCTs, one comparative observational study**<br>Meta-analysis found no effect of rFVIIa on mortality (risk difference: low-dose group: 0.031 [95% CI -0.086 to 0.024], medium-dose group: 0.020 [95% CI -0.076 to 0.036], high-dose group: 0.027 [95% CI -0.121 to 0.068]). No difference in mortality was found in the observational study. | **Assessment: Current**<br>An expert reviewer suggested an article[25] on using rFVIIa to treat cerebral hemorrhage in acute promyelocytic leukemia individuals, but it did not meet inclusion criteria (was not a randomized or observational study). | No studies were identified. |
| **Outcome: Arterial Thromboembolic Events (Arterial TEs)**<br>**SOE: Moderate**<br>**Four RCTs, one comparative observational study**<br>Meta-analysis found significantly higher rates of arterial thromboembolic events with medium and high doses of rFVIIa compared to usual care, and a similar, but non-significant, finding for low doses of rFVIIa (risk difference: low dose 0.025 [95% CI -0.004 to 0.053], medium dose 0.035 [95% CI 0.008 to 0.062], high dose 0.063 [95% CI 0.011 to 0.063]). The observational study only identified one TE, in the rFVIIa group. | **Assessment: Current***<br>Two studies examined the association between rFVIIa use and risk of arterial thromboembolic events (arterial TEs).<br>• One RCT[4] (n=841) demonstrated an association between higher doses of rFVIIa and arterial TEs as compared to no-rFVIIa group (odds ratio=2.14; p=0.031).<br>• *A meta-analysis of 35 total RCTs (four among spontaneous central nervous system bleeding individuals)[3] found a similar association between higher doses of rFVIIa and arterial TEs compared to no-rFVIIa group (odds ratio=1.67 with 95% CI: 1.03, 2.69; p= 0.04).* | No studies were identified. |
| **Outcome: Venous Thromboembolic Events**<br>**SOE: Moderate**<br>**Four RCTs**<br>Meta-analysis found no difference between groups in venous TE (risk difference: low dose 0.010 [95% CI -0.018 to 0.038], medium dose -0.004 [95% CI -0.030 to 0.022], high dose -0.012 [95% CI -0.049 to 0.026]). | **Assessment: Current**<br>No studies were identified. | A RCT[5] (n=21) among individuals receiving surgery for spontaneous supratentorial intracerebral hemorrhage compared the use of rFVIIa (100 mcg/KG b.w.) to placebo and found similar frequencies of deep venous thrombosis among both groups (18-30 hours: 7.7% vs 16.6%, p=1.0; 5-7 days (cumulative): 18.2% vs. 16.6%, p=1.0) |
| **Outcome: Functional outcomes (modified Rankin Scale)**<br>**SOE: Moderate** | **Assessment: Current**<br>No studies were identified. | No studies were identified. |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) |
|---|---|---|
| **4 RCTs**<br>Meta-analysis found no effect of rFVIIa on modified Rankin Scale (mRS) (risk difference: low dose -0.024 [95% CI -0.093 to 0.045], medium dose -0.029 [95% CI -0.099 to 0.041], high dose -0.040 [95% CI -0.154 to 0.075]). | | |
| **Outcome: Change in Hematoma volume**<br>**SOE: Moderate**<br>**Four RCTs**<br>Meta-analysis found significant reductions in relative hematoma expansion in the rfVIIa group compared to usual care at all dosing levels (standardized mean difference: low dose -0.146 [95% CI -0.291 to -0.001], medium dose -0.240 [95% CI -0.385 to -0.095], high dose -0.334 [95% CI -0.579 to -0.090]). | **Assessment: Current**<br>No studies were identified. | A RCT[5] (n=21) among individuals receiving surgery for spontaneous supratentorial intracerebral hemorrhage compared the use of rFVIIa (100 mcg/KG b.w.) to placebo and found similar reductions in intracerebral hemorrhage volumes following hematoma evacuation at 18-30 hours (mean difference 2.1 mL, 95% confidence interval -12.1 to 16.2, P=0.76 [0.03 mL after adjustment for baseline value]). |

*Abbreviations:* BW=By Weight; CI=Confidence Interval; mRS=Modified Rankin Scale; RCT=Randomized Controlled Trial; rFVIIa=Recombinant Factor Seven-A; SOE=Strength of Evidence; TE=Thromboembolic Event

*Studies in italics*= the prior surveillance assessment identified two meta-analyses[3,11]; however upon further review, we discovered that all studies included in these meta-analysis, for these indications, appeared in the original systematic review. Thus, we are not considering these meta-analyses in the determination of currency.

* Indicates the assessment of currency was changed from "possibly out of date" to "current" in the current review due to the removal of the two meta-analyses[3,11] whose results were previously included in the original systematic review.

Table 3. Key Question 3a: Use of rFVIIa for Selected Indications in Individuals With/Undergoing Massive Bleeding from Trauma (Body Trauma)

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) |
|---|---|---|
| **Outcome: Mortality (30 days)**<br>**SOE: Low**<br>**Two RCTs, three comparative observational studies**<br>• Among individuals who survived at least 48 hours, RCTs note no difference between rfVIIa and usual care in 30-day mortality. Evidence from observational studies weakly favored rFVIIa. | **Assessment: Possibly out of date**<br>Three RCTs and one observational study examined mortality rates associated with rFVIIa versus no-rFVIIa groups.<br>• One RCT recommend by an expert reviewer[8] (n=560) compared rFVIIa use to placebo and found no significant difference in 30-day mortality between groups (12.2% vs 11.1%; p= 0.61). | No studies were identified. |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) |
|---|---|---|
| Of note, studies had differing exclusion criteria for 48-hour mortality, and none of them were sufficiently powered to detect differences in 30-day mortality. | • A second RCT[6] (n=2,050) found similar mortality rates among rFVIIa and no-rFVIIa groups (20.0% vs 14.3%; p>0.05). However, this study also demonstrated significantly increased mortality rate with the use of rFVIIa in regression analysis (OR: 1.67, 95% CI: 1.08 to 2.60; p=0.02).<br>• A third RCT[9] (n=573) found no difference in 30-day mortality between rFVIIa and no-rFVIIa groups for individuals with blunt trauma (11.0% vs10.7%, p= 0.93) or for individuals with penetrating trauma (18.2% vs13.2%; p= 0.40).<br>A retrospective cohort study recommended by an expert reviewer[7] found no difference in mortality for rFVIIa compared to no-rFVIIa in terms of transfusions less than/equal to 20 units (24-hour: 25% vs 24%; 30-day: 25% vs 42%) or 21 to 30 units (24-hour: 33% vs 47%, 30-day: 55% vs 50%). However, for initial requirement of more than/equal to 30 units of RBCs, 24-hour mortality (26% vs 64%, P = 0.02) was significantly decreased in individuals that received rFVIIa compared with those who did not. These mortality differences were not maintained at 30 days (68% vs 71%). | |
| **Outcome: Thromboembolic Events (TEs)**<br>**SOE: Low**<br>**Two RCTs, three comparative observational studies**<br>• Studies found no difference between rFVIIa and usual care groups on risk of TEs. However, the absolute number of events was low, so the studies were likely underpowered to detect any difference between groups. | **Assessment: Current**<br>Two studies found no difference between rFVIIa and no-rFVIIa groups on risk of TEs.<br>• *A meta-analysis of 35 RCTs (one among body trauma individuals) reported an odds ratio 1.39 for TEs (rFVIIa vs no-rFVIIa group) (95% CI: 0.69 to 2.77; p= 0.36)*[3]<br>A RCT[8] recommend by an expert reviewer (n=560) found no significant difference between rFVIIa and no-rFVIIa groups in risk of arterial or venous TEs. | A retrospective cohort study[13] (n=152) of individuals receiving off label rFVIIa in a large academic center (2005-2012) compared rates of TE by low vs high dose (cumulative dose of <50 mcg/kg vs. ≥50 mcg/kg respectively). Of those who received rFVIIa for a trauma-related indication (penetrating or blunt; n=36), 2/24 receiving a low dose, and 1/12 receiving a high dose experienced a TE. There was no significant difference in TE by dose. |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) |
|---|---|---|
| **Outcome: Units of RBCs Transfused**<br>**SOE: Low**<br>**Two RCTs, one comparative observational studies**<br>• For blunt trauma individuals, one RCT found a significant reduction in RBC transfusions for rFVIIa compared to no-rFVIIa. Another RCT among penetrating trauma individuals found similar but non-significant reductions in RBC transfusions. The observational study found an increase in transfusion requirements associated with rFVIIa compared to usual care.<br>Of note, comparisons across studies are difficult due to differing exclusion criteria for early in-hospital mortality. | **Assessment: Current**<br>A RCT and two observational studies examined units of RBCs transfused for rFVIIa vs no-rFVIIa groups<br>• A RCT[9] (n=573) found that blunt trauma individuals who received rFVIIa used significantly fewer RBC units over 48 hours compared to no-rFVIIa group (\(mean±SD) 7.8 ± 10.6 versus 9.1±11.3; p= 0.04). However, penetrating trauma individuals who received rFVIIa had non-significantly reduced RBC units over 48 hours compared to no-rFVIIa (5.0±7.4 versus 6.8 ± 6.9; p= 0.11.7)<br>• A retrospective cohort study [7] (n=228) recommend by an expert reviewer examined rFVIIa compared to no-rFVIIa among massively transfused individuals. The study found reduced RBC units in rFVIIa compared to no-rFVIIa over 6 hours (mean: 35.6±2.6 vs. 25.6±0.7; p=0.001) and 24 hours (mean: 38.6±2.9 vs. 28.0±1.0; p=0.00).<br>Another retrospective cohort study[6] found no difference between those who received rFVIIa and no-rFVIIa in the number and range of RBC units used (number(range); rFVIIa: 10(6–16) vs no-rFVIIa 10(4–17); p<NS) | No studies were identified. |
| **Outcome: Acute respiratory distress syndrome (ARDS)**<br>**SOE: Low**<br>**Two RCTs, one comparative observational study**<br>• One blunt trauma RCT identified a significantly lower rate of ARDS in the rFVIIa group compared to the usual care group, while a penetrating trauma RCT | **Assessment: Current**<br>No studies were identified. | No studies were identified. |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) |
|---|---|---|
| and the observational study together suggested a trend in the same direction. Event rates for ARDS were low, so the studies were likely underpowered to detect any difference between groups. | | |

*Abbreviations:* ARDS=Acute Respiratory Distress Syndrome; RBC=Packed Red Blood Cells; RCT=Randomized Controlled Trial; rFVIIa-Recombinant Factor Seven-A; SOE=Strength of Evidence; TE=Thromboembolic Event
*Studies in italics*= the prior surveillance assessment identified two meta-analyses[3,11]; however upon further review, we discovered that all studies included in these meta-analysis, for these indications, appeared in the original systematic review. Thus, we are not considering these meta-analyses in the determination of currency.

Table 4. Key Question 3b. Use of rFVIIa for Selected Indications in Individuals With/Undergoing Massive Bleeding from Trauma (Brain Trauma) i.e., Traumatic Brain Injury [TBI])

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) |
|---|---|---|
| **Outcome: Mortality (15 days)**<br>**SOE: Low**<br>**One RCT, one comparative observational study**<br>• The RCT found no difference between groups in mortality at 15 days, with rates of 11% in each group. The observational study found a reduced mortality with rFVIIa compared to usual care but this was a non-significant finding: 33.3% vs 52.9% in the two groups, respectively.<br>• The findings in both studies are limited by low event rates. | **Assessment: Current**<br>A retrospective cohort study[10] (n=28) found no significant differences between rFVIIa and no-rFVIIa on mortality (50% vs 29%; p=0.22). | Two studies found no difference between rFVIIa and no-rFVIIa groups on mortality.<br>• A retrospective cohort study[15] (n=86) found no significant difference between individuals who received low-dose rFVIIa and matched no-rFVIIa groups on mortality.<br>• A prospective cohort study[17] (n=87) of individuals with TBI and coagulopathy found a non-significant reduction in mortality among those who received low-dose rFVIIa therapy compared to no-rFVIIa. |
| **Outcome: Thromboembolic events (TEs) (72 hours)**<br>**SOE: Low**<br>**One RCT, one comparative observational study**<br>• The RCT found TE event rates in rFVIIa vs usual care were 16.4% and 5.6% respectively. Half of the events in the | **Assessment: Current**<br>Two studies assessed the association between rFVIIa and TEs as compared to no-rFVIIa groups.<br>• *A meta-analysis of 35 total RCTs (one among TBI individuals) reported no difference between rFVIIa and placebo in rates of arterial TEs (3.3% vs 2.8%).*[3] | A retrospective cohort study[15] (n=86) found no occurrence of thromboembolic events in either rFVIIa or matched no-rFVIIa groups. |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) |
|---|---|---|
| rFVIIa group consisted of deep vein thrombosis, all of which were symptomatic. The observational study found TE event rates in rFVIIa vs usual care were 22.2% and 17.6% respectively. One of these events was deep vein thrombosis, which occurred in the usual care group.<br>• The findings in both studies are limited by low event rates. | • A retrospective cohort study[10] (n=28) of individuals with TBI undergoing emergent craniotomy reported no TE complications in either the rFVIIa or no-rFVIIa groups. | |
| **Outcome: Hematoma volume change**<br>**SOE: Low**<br>**One RCT**<br>• One RCT found a non-significant reduction in hematoma volume change in the rFVIIa group compared to no-rFVIIa group (7.0 mL (SD 12.9) versus 10.4 mL (25.0), respectively). | **Assessment: Current**<br>No studies were identified. | No studies were identified. |
| **Outcome: RBC Transfusion Requirement**<br>No studies reported on this outcome. | **Assessment: Possibly out of date**<br>An retrospective study[10] (n=28) among individuals with TBI undergoing emergent craniotomy found a significant reduction of RBC units in individuals receiving rFVIIa versus no-rFVIIa (median(range) of units: preoperative: 0 (0–2) versus 4 (2–8); p= 0.001; intraoperative: 1 (0–2) versus 5 (2–8) ; p=0.002; postoperative: 1 (0–2) versus 3 (2–5); p= 0.002; and total: 4 (1–5) versus 14 (10–17); p= 0.001.) | No studies were identified. |
| **Outcome: ICU length of stay**<br>No studies reported on this outcome. | No studies were identified. | A retrospective cohort study[15] (n=86) found no significant difference between individuals who received low-dose rFVIIa and matched no-rFVIIa individuals on length of ICU stay. |

*Abbreviations:* ICU=Intensive Care Unit; RCB=Packed Red Blood Cells; RCT=Randomized Controlled Trials; rFVIIa=Recombinant Factor Seven-A; SD=Standard Deviation; SOE=Strength of Evidence; TBI=Traumatic Brain Injury; TE=Thomboembolic Event;
*Studies in italics*= the prior surveillance assessment identified two meta-analyses[3,11]; however upon further review, we discovered that all studies included in these meta-analysis, for these indications, appeared in the original systematic review. Thus, we are not considering these meta-analyses in the determination of currency.

Table 5. Key Question 4a: Use of rFVIIa for Selected Indications in Individuals With/Undergoing Liver Transplantation

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) |
|---|---|---|
| **Outcomes: Mortality**<br>**SOE: Low**<br>**Three RCTs**<br>• The RCTs found no difference in mortality rates between groups, although the studies were not sufficiently powered for this outcome. | **Assessment: Current**<br>*A meta-analysis of four RCTs[11] (two among liver transplantation individuals and two among liver resection individuals) recommended by an expert reviewer found no difference in mortality between rFVIIa and placebo groups (OR=0.96, 95% CI: 0.35, 2.62).* | An retrospective cohort study[16] (n=183) compared the use of rFVIIa preemptively or intraoperatively to a matched no-rFVIIa group and found that individuals who received rFVIIa preemptively had similar mortality rates as the no-rFVIIa group, but individuals who received rFVIIa intraoperatively had increased mortality rates at 30 days and one year. |
| **Outcomes: Thromboembolic events**<br>**SOE: Low**<br>**Three RCTs, one comparative observational study**<br>• The RCTs found no differences in TEs between groups. The observational study only reported one thromboembolic event - thrombosis of the hepatic artery in a patient who received rFVIIa. | **Assessment: Current**<br>No studies were identified. | No studies were identified. |
| **Outcomes: Units of RBCs transfused in 24-hour post-operative period**<br>**SOE: Low**<br>**Three RCTs, one comparative observational study**<br>One RCT found a significant reduction in RBC units with rFVIIa, one RCT found a non-significant reduction in RBC units with rFVIIa, and one RCT found no difference between rFVIIa versus usual care. The observational study found significantly lower RBC transfusion requirements with rFVIIa. | **Assessment: Current***<br>*A meta-analysis of four RCTs[11] (two among liver transplantation individuals and two among liver resection individuals) recommended by an expert reviewer found no difference in units of RBCs between rFVIIa and placebo (Mean difference: 0.32, 95% CI: -0.08, 0.72).* | An retrospective cohort study[16] (n=183) compared the use of rFVIIa preemptively or intraoperatively to a matched no-rFVIIa group and found that individuals who received rFVIIa intraoperatively required more blood products than individuals receiving rFVIIa preemptively or the no-rFVIIa group. |
| **Outcomes: Operating Room Time**<br>**SOE: Low**<br>**One RCT, one comparative observational study**<br>One RCT identified a significant difference between groups in operating room time, with | **Assessment: Current**<br>No studies were identified. | No studies were identified. |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) |
|---|---|---|
| transplantation taking over 200 minutes less in the rFVIIa group compared to placebo. None of the other studies identified a significant difference between groups | | |
| **Outcomes: ICU length of stay**<br>**SOE: Low**<br>**Three RCTs**<br>Three RCTs found no difference between groups in ICU length of stay. | **Assessment: Current**<br>No studies were identified. | An retrospective cohort study[16] (n=183) compared the use of rFVIIa preemptively or intraoperatively to a matched no-rFVIIa group and found that individuals who received rFVIIa intraoperatively had longer ICU stays than those receiving rFVIIa preemptively or the no-rFVIIa group. |

*Abbreviations:* CI=Confidence Interval; ICU=Intensive Care Unit; RBC=Packed Red Blood Cells; RCT=Randomized Controlled Trial; rFVIIa=Recombinant Factor Seven-A; SOE=Strength of Evidence; TE=Thromboembolic Event
*Studies in italics*= the prior surveillance assessment identified two meta-analyses[3,11]; however upon further review, we discovered that all studies included in these meta-analysis, for these indications, appeared in the original systematic review. Thus, we are not considering these meta-analyses in the determination of currency.
*Indicates the assessment of currency was changed from "possibly out of date" to "current" in the current review due to the removal of the two meta-analyses[3,11] whose results were previously included in the original systematic review.

Table 6. Key Question 4b.i. Use of rFVIIa for Selected Indications in Individuals With/Undergoing Cardiac Surgery (Adult Cardiac Surgery)

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) |
|---|---|---|
| **Outcomes: Mortality (in-hospital)**<br>**SOE: Low**<br>**Two RCTs, four comparative observational studies, four meta-analyses**<br>Meta-analysis of good-quality RCTs and observational studies found no difference in mortality between rFVIIa and usual care (risk difference 0.007; 95% CI -0.049 to 0.063) | **Assessment: Current**<br>No studies were identified. | No studies were identified. |
| **Outcomes: Thromboembolic events**<br>**SOE: Moderate**<br>**Two RCTs, four comparative observational studies, four meta-analyses**<br>Meta-analysis of RCTs and good quality observational studies identified a higher rate of | **Assessment: Current**<br>*A meta-analysis[3] of 35 RCTs (two among adult and one among pediatric cardiac surgery individuals) found no significant effect of rFVIIa on arterial TE event rates compared to placebo (odds ratio=1.59, 95% CI: 0.47, 5.34; p= 0.45).* | No studies were identified. |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) |
|---|---|---|
| thromboembolic events in the rFVIIa group compared to the no-rFVIIa group (risk difference 0.053; 95% CI 0.01 to 0.096) | | |
| **Outcomes: Units of RBCs transfused in 24 hours**<br>**SOE: Low**<br>**One RCT, three comparative observational studies**<br>A RCT and a good quality observational study found a non-significant and significant difference between groups that favored rFVIIa use over no-rFVIIa groups, respectively (p values 0.11 and <0.001). One additional observational study found no difference between groups, and another found a significant effect against the rFVIIa group (i.e., increased transfusions with treatment). | **Assessment: Current**<br>No studies were identified. | No studies were identified. |
| **Outcomes: ICU length of stay**<br>**SOE: Low**<br>**One RCT, four comparative observational studies**<br>One RCT found no significant difference between groups in ICU length of stay. Findings among observational studies were inconsistent: one cohort study found a significantly longer ICU length of stay for rFVIIa individuals but two others had significant and non-significant findings in the opposite direction, respectively. A fourth cohort study found no difference between groups. | **Assessment: Current**<br>No studies were identified. | No studies were identified. |
| **Outcome: Operating room time**<br>No studies reported on this outcome. | **Assessment: Current**<br>A retrospective chart review[12] (n=24) recommended by an expert reviewer reported lesser median operating room time for rFVIIa group versus reoperation for refractory bleeding after surgery group, however, the data were not reported. | No studies were identified. |

*Abbreviations:* CI=Confidence Interval; ICU=Intensive Care Unit; RBC=Packed Red Blood Cells; RCT=Randomized Controlled Trial; rFVIIa=Recombinant Factor Seven-A; SOE=Strength of Evidence; TE=Thromboembolic Event
*Studies in italics*= the prior surveillance assessment identified two meta-analyses[3,11]; however upon further review, we discovered that all studies included in these meta-analysis, for these indications, appeared in the original systematic review. Thus, we are not considering these meta-analyses in the determination of currency.

Table 7.Key Question 4b.ii. Use of rFVIIa for Selected Indications in Patient With/Undergoing Cardiac Surgery (Pediatric Cardiac Surgery)

| **Conclusions From Original Systematic Review (May 2010) Link to report** | **Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report** | **Literature Analysis (December 2015)** |
|---|---|---|
| **Outcomes: Mortality (in-hospital)**<br>**SOE: Insufficient**<br>No studies were identified. | **Assessment: Current**<br>A retrospective matched case-control study [20] (n=75) found no significant difference between individuals receiving rFVIIa and a matched no-rFVIIa group on mortality. | A retrospective matched case-control study [14] (n=135) of individuals who received rFVIIa (during or after cardiac surgery) and matched no-rFVIIa group found no significant differences in mortality rates (16% vs 9.5%, p=.208). |
| **Outcomes: Thromboembolic events**<br>**SOE: Insufficient**<br>**One RCT**<br>One RCT identified no thromboembolic events in either rFVIIa or usual care groups. | **Assessment: Current**<br>A retrospective matched case-control [20] (n=75) found no significant differences between individuals receiving rFVIIa and a matched no-rFVIIa group on rate of TE (8% versus 4%; p=NR). | A retrospective matched case-control study [14] (n=135) of individuals who received rFVIIa (during or after cardiac surgery) and matched no-rFVIIa group found no significant differences in the rate of thrombosis (20% vs 28%, p=.540). |
| **Outcomes: Units of Whole Blood/RBC transfusion**<br>**SOE: Insufficient**<br>**One RCT**<br>One RCT found a non-significant decrease in transfusion requirements for RBCs and/or whole blood in the rFVIIa group compared to no-rFVIIa groups. | **Assessment: Current**<br>A retrospective matched case-control [20] (n=75) found no significant differences between individuals receiving rFVIIa and a matched no-rFVIIa group on RBC transfusion requirements (93.2 mL/kg versus 108.3 mL/kg; p = 0.225). | No studies were identified. |
| **Outcomes: Time to chest closure**<br>**SOE: Insufficient**<br>**One RCT**<br>One RCT found that rFVIIa individuals had a longer time to chest closure than did no-rFVIIa groups (98.8 minutes (SE 27.3) versus 58.3 minutes (SE 29.2), p=0.026). | **Assessment: Current**<br>No studies were identified. | No studies were identified. |

*Abbreviations:* NR=Not Reported; RBC=Packed Red Blood Cells; RCT=Randomized Controlled Trial; rFVIIa=Recombinant Factor Seven-A; SE=Standard Error; SOE=Strength of Evidence

Table 8. Key Question 4c. Use of rFVIIa for Selected Indications in Patient With/Undergoing Prostatectomy

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) |
|---|---|---|
| **Outcomes: Mortality (10 day)**<br>**SOE: Insufficient**<br>**One RCT**<br>One RCT reported no deaths in either rFVIIa or no-rFVIIa groups. | **Assessment: Current**<br>No studies were identified. | No studies were identified. |
| **Outcomes: Thromboembolic events**<br>**SOE: Insufficient**<br>**One RCT**<br>One RCT reported a single TE (myocardial infarction) in the 20 µg/kg dose of rFVIIa group. | **Assessment: Current**<br>No studies were identified. | No studies were identified. |
| **Outcomes: Units of RBCs transfused**<br>**SOE: Insufficient**<br>**One RCT**<br>One RCT found significantly reduced RBC transfusion requirements in the rFVIIa group compared to usual care. | **Assessment: Current**<br>No studies were identified. | No studies were identified. |
| **Outcomes: Operative Room time**<br>**SOE: Insufficient**<br>**One RCT**<br>One RCT found significantly reduced operating room time in the rFVIIa group compared to usual care | **Assessment: Current**<br>No studies were identified. | No studies were identified. |

*Abbreviations:* RBC=Packed Red Blood Cells; RCT=Randomized Controlled Trial; rFVIIa=Recombinant Factor Seven-A; SOE=Strength of Evidence; TE=Thromboembolic Event

**Abstracts from Relevant Literature/References**

17. Bucklin, M. H., et al. (2014). "The effects of recombinant activated factor VII dose on the incidence of thromboembolic events in patients with coagulopathic bleeding." Thromb Res 133(5): 768-771.

INTRODUCTION: Previous studies have suggested the used of off-label recombinant factor VII (rFVIIa) increases the risk of thromboembolic events, but the effect of the dose of rFVIIa is not well described in the literature. MATERIALS AND METHODS: All adult patients that received off-label rFVIIa from 2005-2012 were included in this single-center, retrospective cohort study. The primary endpoint was the incidence of a thromboembolic event in the low dose (<50 mcg/kg) compared to the high dose (>/=50

mcg/kg) cohort. Secondary endpoints compared time to thromboembolic event, incidence of arterial compared to venous events, and mortality. RESULTS: There were 152 patients that received rFVIIa during the study period with 66 in the low dose cohort and 86 in the high dose cohort. Mean total dose of rFVIIa was 30.2 mcg/kg (SD +/- 9.5 mcg/kg) in the low dose and 99.8 mcg/kg (SD +/- 64.7 mcg/kg) in the high dose cohort (p=0.0001). The overall incidence of thromboembolic events was 12.5%. There were 12 (14%) events in the low dose cohort and seven (10.6%) in the high dose cohort, RR=0.76 (95% CI 0.31-1.82). There were no differences in any of the secondary outcomes. A higher incidence of thromboembolic events in cardiothoracic surgery (20.8%) and penetrating trauma patients (21.4%) was seen compared to the remaining cohort (6.7%). CONCLUSIONS: No significant difference in the incidence of thromboembolic events was seen between low dose versus high dose rFVIIa over a seven year period at our institution. However, due to the relatively low overall incidence and a small sample size, type II error may be present.

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16. Imberti, R., et al. (2012). "Intraoperative intravenous administration of rFVIIa and hematoma volume after early surgery for spontaneous intracerebral hemorrhage: a randomized prospective phase II study." Minerva Anestesiol 78(2): 168-175.

BACKGROUND: Surgery of spontaneous supratentorial intracerebral hemorrhage (ICH), especially if performed early, can be complicated by rebleeding, a condition that can worsen the outcome. We evaluated the effect of recombinant activated factor VII (rFVIIa) on postoperative rebleeding. METHODS: In this randomized, open-label, single-blinded study, 21 patients with spontaneous supratentorial ICH diagnosed by computed tomography (CT) scan were treated with intravenous rFVIIa (100 mcg/Kg b.w., N=13) or placebo (N=8). Hematoma volume was assessed using CT scan immediately, 18-30 hours, and 5-7 days after hematoma evacuation. The primary endpoint was a hematoma volume at 18-30 hours after surgery. All CT scans were evaluated at one center by the same investigator who was unaware of the treatment. Hematoma volume was measured using dedicated software. RESULTS: At baseline, the hematoma volume was 59.2+/-27.4 and 71.5+/-32.1 mL in the rFVIIa and placebo group, respectively. Hematoma evacuation resulted in significantly smaller ICH volumes that were similar in the rFVIIa and placebo group at 18-30 hours after surgery (15.9+/-14.2 mL and 18+/-15.1 mL, respectively; mean difference 2.1 mL, 95% confidence interval -12.1 to 16.2, P=0.76 (0.03 mL after adjustment for baseline value)). The frequencies of deep venous thrombosis, myocardial infarction, troponin I elevation and cerebral ischemia were similar in both groups. CONCLUSION: In this pilot study, intraoperative, intravenous rFVIIa administration did not modify hematoma volume after early ICH surgery. However, the 95% CI was wide, which indicates considerable uncertainty. Therefore, our results do not disprove the potential benefit of rFVIIa administration, which could be shown in a larger study.

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21. Martinez Lopez, M. C., et al. (2013). "[Risk assessment of thrombotic events after the use of activated factor VII]." An Pediatr (Barc) 79(3): 177-181.

INTRODUCTION: The objective of this study was to analyze the incidence of thrombotic complications related to recombinant human factor viia (rFVIIa) therapy for severe postoperative bleeding in cardiac surgery. MATERIAL AND METHODS: A retrospective

matched case-control study was conducted over two years, including 72 children admitted to intensive care unit and treated with rFVIIa because of a severe bleeding during or after cardiac surgery. A control group of 63 patients was chosen, who were statistically comparable in sex, weight, diagnosis, surgical risk according RASCH-1 score, and surgical characteristics, was chosen. RESULTS: There were no significant differences between cases and controls either in the rate of thrombosis (20% vs 28%, P=.540), or in the mortality rate (16% vs 9.5%, P=.208). CONCLUSIONS: In our study, the rFVIIa therapy was shown to be useful in controlling severe operative bleeding in pediatric cardiac surgery, but does not seem to increase the risk of thrombotic complications or mortality rate in the postoperative period.

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18. Pei, B. B., et al. (2013). "[Role of small-dose recombinant human coagulation factor VIIa for coagulopathy in patients with isolated traumatic brain injury]." Zhonghua Yi Xue Za Zhi 93(23): 1780-1783.

OBJECTIVE: To explore the role of small-dose recombinant human coagulation factor VIIa (rFVIIa) for coagulopathy in patients with isolated traumatic brain injury. METHODS: A total of 86 isolated traumatic brain patients with coagulopathy were treated at our neurosurgery intensive care unit (NICU) from January 2010 to December 2012. Their trauma registry data included mortality, pre-and post-rFVIIa coagulation parameters. Two-tailed paired t-test was used to determine significant changes in coagulation parameters and other major clinical parameters. RESULTS: Twenty-seven patients made up the low-dose rFVIIa (20 microg/kg) group. And the control group had 59 well-matched subjects. At admission, age, blood pressure, Glasgow coma scale score, hemoglobin, platelets and international normalize ratio were similar in both groups. After treatment, the INR of patients on rFVIIa was lower than that of the conventional treatment group (1.1 +/- 0.2 vs 1.2 +/- 0.2, P < 0.01) and it declined more in the rFVIIa group (0.3 +/- 0.2 vs 0.1 +/- 0.4, P = 0.05). No significant difference existed in mortality or length of stay between two groups.There was no occurrence of subsequent thromboembolic events. CONCLUSION: The application of small-dose rFVIIa can effectively reduce the value of INR and improve the coagulation status of patients. During the course of treatment, no major adverse events occur.

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20. Scheffert, J. L., et al. (2013). "Timing of factor VIIa in liver transplantation impacts cost and clinical outcomes." Pharmacotherapy 33(5): 483-488.

STUDY OBJECTIVE: To investigate the clinical and economic outcomes associated with the use of recombinant factor VIIa (rFVIIa) in perioperative liver transplantation (LT). DESIGN: Retrospective review. SETTING: Academic medical center. PATIENTS: A total of 63 adults who underwent LT between January 2000 and September 2008 and received rFVIIa prior to or during the procedure. Using a propensity-scoring method, these patients were matched in a 1:2 ratio with 120 controls. MEASUREMENTS AND MAIN RESULTS: Of the 473 patients who received any LT during the study period, 63 (13%) received rFVIIa and were matched with propensity score matched controls at a ratio of approximately 1:2. Of those who received rFVIIa, 27 (43%) received preemptive administration and 14 (22%) received intraoperative administration. (The remaining 22 patients received rFVIIa outside of a 12-hour window of time before or after surgery.) Clinical outcomes were similar between the preemptive and the control groups, although patients in the control

group had a shorter length of stay in the intensive care unit (ICU) and incurred fewer expenses. Compared with both the preemptive and the control groups, patients who received rFVIIa intraoperatively required more blood products, longer stays in the ICU, and incurred higher costs. They also had poorer graft survival and decreased overall survival rates at 30 days and 1 year. CONCLUSION: Intraoperative administration of rFVIIa in LT was associated with higher blood product use, lower graft and patient survival rates, longer ICU stays, and higher overall costs compared with preemptive administration. The use of preemptive rFVIIa in select high-risk LT patients may prevent the development of poor clinical outcomes and may be more cost effective compared with intraoperative administration.

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19. Yuan, Q., et al. (2015). "Low-dose recombinant factor VIIa for reversing coagulopathy in patients with isolated traumatic brain injury." J Crit Care 30(1): 116-120.

PURPOSE: The purpose of this study was to investigate the role of low-dose recombinant factor VIIa (rFVIIa) (20 mug/kg) in reversing coagulopathy in patients with isolated traumatic brain injury (TBI). MATERIALS AND METHODS: Patients with isolated TBI and coagulopathy at admission were enrolled prospectively from January 2010 to December 2011. The patients were divided into 2 groups: the rFVIIa and the no-rFVIIa groups. In the rFVIIa group, patients received a single dose of 20 mug/kg rFVIIa intravenously to reverse their coagulopathy in addition to blood products. Patients in the no-rFVIIa group received only blood products to correct the coagulopathy. The clinical outcome variables evaluated included changes in coagulation parameters after administration for reversing coagulopathy, the occurrence of progressive hemorrhagic injury (PHI), intensive care unit length of stay, the incidence of thromboembolic complications, inhospital mortality, and 90-day Glasgow Outcome Scale. RESULTS: Eighty-seven patients were ultimately included in this study. Of them, 49 patients were treated with blood products alone, whereas 38 patients also received rFVIIa to reverse their coagulopathy. The improvement in international normalized ratio was greater in the rFVIIa group (0.26 [0.18-0.39]) than in the no-rFVIIa group (0.06 [-0.11 to 0.30]) (P = .001). In addition, the improvement in lactate was also greater in the rFVIIa group (0.33 [-0.18 to 0.54]) than in the no-rFVIIa group (0.04 [-0.25 to 0.20]) (P = .029). During the period after we began to correct the coagulopathy, PHI occurred in 19 patients (38.8%) in the no-rFVIIa group, which was significantly higher than that in the rFVIIa group (7, 18.4%; P = .040). The rate of cerebral infarction was similar in both groups (10.2% vs 5.3%). There was a trend indicating that low-dose rFVIIa therapy was associated with a lower mortality, but the association was not statistically significant (P = .266). CONCLUSIONS: The use of low-dose rFVIIa (20 mug/kg) is effective for correcting coagulopathy in patients with TBI without an increase in thromboembolic events. Moreover, it is more effective for preventing the occurrence of PHI.

## Appendix E. Summary Table

No relevant FDA warnings were identified.

Table 1. Key Question 1: Indications, Populations, and Characteristics of Comparative Studies of Off-Label rFVIIa Use?

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
|---|---|---|---|---|
| **Indications and populations of comparative studies:** Off-label rFVIIa use was examined in 24 RCTs and 31 comparative observational studies across a variety of clinical indications, including cardiac surgery (12 studies), trauma (nine studies), intracranial hemorrhage (ICH) (eight studies), liver transplantation (eight studies),prostatectomy (one study), other liver disease (five studies), obstetrics/gynecology (three studies), hematology/oncology (three studies), and other surgery (six studies). There were prominent community uses that lacked studies, such as primary clotting disorders other than hemophilia, secondary clotting disorders, and gastrointestinal bleeding not related to liver disease. Other indications with no studies included aortic | **Indications and populations of comparative studies:** Indications for off-label rFVIIa use were consistent in the 2012 surveillance report as in the original systematic review. Studies examined rFVIIa use *for intracranial hemorrhage (three studies[3,4,19]), body trauma (eight studies[3,6-10,18,19]), traumatic brain injury (one study[3]) and those undergoing cardiac surgery (two studies[3,12,20]) and liver transplantation[11].*<br><br>**Characteristics of comparative studies:** Consistent with the original systematic review, the 2012 literature search identified both RCTs[4,8,9,18,21], and observational studies[6,7,10,12,19,20,22]. One systematic review[23] and *two meta-analyses*[3,11] were also identified. Also consistent with the original systematic review, | **Indications and populations of comparative and registry studies:** In general, we identified indications for off-label rFVIIa use that were consistent with the original systematic review: intracranial hemorrhage (one comparative study[5] and one registry study),[2] body trauma (one comparative study[13]), traumatic brain injury (two comparative studies[15,17]), liver transplantation (one comparative study[16]), adult cardiac surgery (one registry study[2]), and pediatric cardiac surgery (one comparative study[14]). The registry study[2] also examined off-label rFVIIa use for other surgery, obstetric hemorrhage, and hematology/oncology.<br><br>**Characteristics of comparative and registry studies:** Most of studies included in this | Experts did not comment on the currency of this conclusion. One expert was surprised there were no findings from the obstetric literature, however the original systematic review included three retrospective comparative studies on rFVIIa use in obstetrics/gynecology (see the first column for details). The other expert suggested a registry study[2] that was previously excluded from our literature analysis that we decided to include (see the third column for details) and a RCT[26] among women with severe postpartum | Conclusions are likely current. |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
|---|---|---|---|---|
| aneurysm, other vascular procedures, and neonatal use (beyond cardiac surgery). Many studies examined only prophylactic use of rFVIIa for clinical indications where treatment or end-stage use may also be frequent. Individuals included in the comparative studies were generally younger and had lower clinical acuity in comparison to individuals in community practice.<br><br>**Characteristics of comparative studies:** With the exception of use in ICH, study sample sizes were small (median of 24 treated individuals). Studies of ICH included two large RCTs of almost 900 individuals treated with rFVIIa. Dosage varied from 5 to 956 mcg/kg of patient weight, and only for intracranial hemorrhage was there a sufficient range of doses to assess the impact of rFVIIa dosing on outcomes. Most studies used indirect endpoints as their primary outcomes, particularly red blood cell (RBC) transfusion requirements, blood loss, and | a wide range of ages (24-76 years old) and dosages of rFVIIa (5-360 µg/kg of patient weight) were represented. The sample size of included studies ranged from 169[18] to *1,397*[3] among RCTs and 24[12] to 2,050[6] in observational studies, which is consistent with the range found in the original review. Also consistent with the original systematic review, most studies reported direct outcomes, such as *thromboembolic events*[3,4,6,8,10,11,19,20,23] *and mortality.*[6-8,10,11,18,21,23] | surveillance report were observational; only one RCT[5] was identified. Sample sizes ranged from a minimum of n= 21[5] to n=3,446 individuals.[2] Consistent with the original review, studies varied in the dosage of rFVIIa administered, and one identified study compared high and low doses[13]. Consistent with the original review, most studies reported direct outcomes, such as mortality[2,14-17,24] and thromboembolic events (TEs).[2,5,13,14,24]<br><br>Note: Upon further consideration of the limitations of examining only comparative studies for the purpose of describing indications of off-label rFVIIa use, we decided to include registry studies for this question. This decision occurred after sending literature search findings to experts. We included one additional study [2] as a result of this decision, which is described above. | hemorrhage that was previously excluded from our analysis because it examined human, rather than recombinant, FVIIa. | |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
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| duration of surgery or Intensive Care Unit (ICU) stay. Direct outcomes, such as mortality, functional status, or thromboembolic events, were frequently reported, but most studies were individually underpowered to evaluate them.<br><br>Note: The form we sent to experts included a list of the off-label indications that comprised 69% of all identified comparative studies (cardiac surgery, trauma, intracranial hemorrhage, liver transplantation, and prostatectomy). The form did not include a list of the indications that comprised the remaining 31% of comparative studies (other liver disease, obstetrics/gynecology, hematology/oncology, and other surgery). We have added these additional 4 indications to this table (see "indications and populations of comparative studies" above) for clarification purposes. | | | | |

*Abbreviations:* ICH=Intracranial Hemorrhage; ICU=Intensive Care Unit; RBC=Packed Red Blood Cells; RCT=Randomized Controlled Trial; rFVIIa=Recombinant Factor Seven-A; TE=Thromboembolic Events

*Studies in italics*= the prior surveillance assessment identified two meta-analyses[3,11]; however upon further review, we discovered that all studies included in these meta-analysis, for these indications, appeared in the original systematic review. Thus, we are not considering these meta-analyses in the determination of currency.

Table 2. Key Question 2: Use of rFVIIa for Selected Indications in Individuals With/Undergoing Intracranial Hemorrhage

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
|---|---|---|---|---|
| **Outcome: Mortality (90 day)**<br>**SOE: Moderate**<br>**Four RCTs, one comparative observational study**<br>Meta-analysis found no effect of rFVIIa on mortality (risk difference: low-dose group: 0.031 [95% CI -0.086 to 0.024], medium-dose group: 0.020 [95% CI -0.076 to 0.036], high-dose group: 0.027 [95% CI -0.121 to 0.068]). No difference in mortality was found in the observational study. | **Assessment: Current**<br>An expert reviewer suggested an article[25] on using rFVIIa to treat cerebral hemorrhage in acute promyelocytic leukemia individuals, but it did not meet inclusion criteria (was not a randomized or observational study). | No studies were identified. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current. |
| **Outcome: Arterial Thromboembolic Events (Arterial TEs)**<br>**SOE: Moderate**<br>**Four RCTs, one comparative observational study**<br>Meta-analysis found significantly higher rates of arterial thromboembolic events with medium and high doses of rFVIIa compared to usual care, and a similar, but non-significant, finding for low doses of rFVIIa (risk difference: low dose 0.025 [95% CI -0.004 to 0.053], medium dose 0.035 | **Assessment: Current***<br>Two studies examined the association between rFVIIa use and risk of arterial thromboembolic events (arterial TEs).<br>• One RCT[4] (n=841) demonstrated an association between higher doses of rFVIIa and arterial TEs as compared to no-rFVIIa group (odds ratio=2.14; p=0.031).<br>• *A meta-analysis of 35 total RCTs (four among spontaneous central* | No studies were identified. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current. |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
|---|---|---|---|---|
| [95% CI 0.008 to 0.062], high dose 0.063 [95% CI 0.011 to 0.063]). The observational study only identified one TE, in the rFVIIa group. | *nervous system bleeding individuals)[3] found a similar association between higher doses of rFVIIa and arterial TEs compared to no-rFVIIa group (odds ratio=1.67 with 95% CI: 1.03, 2.69; p= 0.04).* | | | |
| **Outcome: Venous Thromboembolic Events**<br>**SOE: Moderate**<br>**Four RCTs**<br>Meta-analysis found no difference between groups in venous TE (risk difference: low dose 0.010 [95% CI -0.018 to 0.038], medium dose -0.004 [95% CI -0.030 to 0.022], high dose -0.012 [95% CI -0.049 to 0.026]). | **Assessment: Current**<br>No studies were identified. | A RCT[5] (n=21) among individuals receiving surgery for spontaneous supratentorial intracerebral hemorrhage compared the use of rFVIIa (100 mcg/KG b.w.) to placebo and found similar frequencies of deep venous thrombosis among both groups (18-30 hours: 7.7% vs 16.6%, p=1.0; 5-7 days (cumulative): 18.2% vs. 16.6%, p=1.0) | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current. |
| **Outcome: Functional outcomes (modified Rankin Scale)**<br>**SOE: Moderate**<br>**4 RCTs**<br>Meta-analysis found no effect of rFVIIa on modified Rankin Scale (mRS) (risk difference: low dose -0.024 [95% CI -0.093 to 0.045], medium dose -0.029 [95% CI -0.099 to 0.041], high dose -0.040 [95% CI -0.154 to 0.075]). | **Assessment: Current**<br>No studies were identified. | No studies were identified. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current. |
| **Outcome: Change in** | **Assessment: Current** | A RCT[5] (n=21) among | One expert felt the | Conclusions are likely |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
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| **Hematoma volume**<br>**SOE: Moderate**<br>**Four RCTs**<br>Meta-analysis found significant reductions in relative hematoma expansion in the rfVIIa group compared to usual care at all dosing levels (standardized mean difference: low dose -0.146 [95% CI -0.291 to -0.001], medium dose -0.240 [95% CI -0.385 to -0.095], high dose -0.334 [95% CI -0.579 to -0.090]). | No studies were identified. | individuals receiving surgery for spontaneous supratentorial intracerebral hemorrhage compared the use of rFVIIa (100 mcg/KG b.w.) to placebo and found similar reductions in intracerebral hemorrhage volumes following hematoma evacuation at 18-30 hours (mean difference 2.1 mL, 95% confidence interval -12.1 to 16.2, P=0.76 [0.03 mL after adjustment for baseline value]). | original conclusion was still current, and the other did not comment on currency. | current. |

*Abbreviations:* BW=By Weight; CI=Confidence Interval; mRS=Modified Rankin Scale; RCT=Randomized Controlled Trial; rFVIIa=Recombinant Factor Seven-A; SOE=Strength of Evidence; TE=Thromboembolic Event

*Studies in italics*= the prior surveillance assessment identified two meta-analyses[3,11]; however upon further review, we discovered that all studies included in these meta-analysis, for these indications, appeared in the original systematic review. Thus, we are not considering these meta-analyses in the determination of currency.

* Indicates the assessment of currency was changed from "possibly out of date" to "current" in the current review due to the removal of the two meta-analyses[3,11] whose results were previously included in the original systematic review.

Table 3. Key Question 3a: Use of rFVIIa for Selected Indications in Individuals With/Undergoing Massive Bleeding from Trauma (Body Trauma)

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
|---|---|---|---|---|
| **Outcome: Mortality (30 days)**<br>**SOE: Low**<br>**Two RCTs, three comparative observational studies**<br>• Among individuals who survived at least 48 hours, | **Assessment: Current***<br>Three RCTs and one observational study examined mortality rates associated with rFVIIa versus no-rFVIIa groups. | No studies were identified. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current.<br><br>Although the 2012 surveillance report determined that an |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
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| RCTs note no difference between rfVIIa and usual care in 30-day mortality. Evidence from observational studies weakly favored rFVIIa.<br>Of note, studies had differing exclusion criteria for 48-hour mortality, and none of them were sufficiently powered to detect differences in 30-day mortality. | • One RCT recommend by an expert reviewer[8] (n=560) compared rFVIIa use to placebo and found no significant difference in 30-day mortality between groups (12.2% vs 11.1%; p= 0.61).<br>• A second RCT[6] (n=2,050) found similar mortality rates among rFVIIa and no-rFVIIa groups (20.0% vs 14.3%; p>0.05). However, this study also demonstrated significantly increased mortality rate with the use of rFVIIa in regression analysis (OR: 1.67, 95% CI: 1.08 to 2.60; p=0.02).<br>• A third RCT[9] (n=573) found no difference in 30-day mortality between rFVIIa and no-rFVIIa groups for individuals with blunt trauma (11.0% vs10.7%, p= 0.93) or for individuals with penetrating trauma (18.2% vs13.2%; p= 0.40).<br>• A retrospective cohort study recommended by an expert reviewer[7] found no difference in mortality for rFVIIa compared to no- | | | RCT[6] and an observational study[7] conflict with the original conclusions, it is our assessment that the conclusion is likely current. |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
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| | rFVIIa in terms of transfusions less than/equal to 20 units (24-hour: 25% vs 24%; 30-day: 25% vs 42%) or 21 to 30 units (24-hour: 33% vs 47%, 30-day: 55% vs 50%). However, for initial requirement of more than/equal to 30 units of RBCs, 24-hour mortality (26% vs 64%, P = 0.02) was significantly decreased in individuals that received rFVIIa compared with those who did not. These mortality differences were not maintained at 30 days (68% vs 71%). | | | |
| **Outcome: Thromboembolic Events (TEs)**<br>**SOE: Low**<br>**Two RCTs, three comparative observational studies**<br>• Studies found no difference between rFVIIa and usual care groups on risk of TEs. However, the absolute number of events was low, so the studies were likely underpowered to detect any difference between groups. | **Assessment: Current**<br>Two studies found no difference between rFVIIa and no-rFVIIa groups on risk of TEs.<br>• *A meta-analysis of 35 RCTs (one among body trauma individuals) reported an odds ratio 1.39 for TEs (rFVIIa vs no-rFVIIa group) (95% CI: 0.69 to 2.77; p= 0.36)*[3]<br>• A RCT[8] recommend by an expert reviewer (n=560) found no significant | A retrospective cohort study[13] (n=152) of individuals receiving off label rFVIIa in a large academic center (2005-2012) compared rates of TE by low vs high dose (cumulative dose of <50 mcg/kg vs. ≥50 mcg/kg respectively). Of those who received rFVIIa for a trauma-related indication (penetrating or blunt; n=36), 2/24 receiving a low dose, and 1/12 receiving a high dose experienced a TE. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current. |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
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| | difference between rFVIIa and no-rFVIIa groups in risk of arterial or venous TEs. | There was no significant difference in TE by dose. | | |
| **Outcome: Units of RBCs Transfused**<br>**SOE: Low**<br>**Two RCTs, one comparative observational studies**<br>• For blunt trauma individuals, one RCT found a significant reduction in RBC transfusions for rFVIIa compared to no-rFVIIa. Another RCT among penetrating trauma individuals found similar but non-significant reductions in RBC transfusions. The observational study found an increase in transfusion requirements associated with rFVIIa compared to usual care.<br>Of note, comparisons across studies are difficult due to differing exclusion criteria for early in-hospital mortality. | **Assessment: Current**<br>A RCT and two observational studies examined units of RBCs transfused for rFVIIa vs no-rFVIIa groups<br>• A RCT[9] (n=573) found that blunt trauma individuals who received rFVIIa used significantly fewer RBC units over 48 hours compared to no-rFVIIa group (\(mean±SD) 7.8 ± 10.6 versus 9.1±11.3; p= 0.04). However, penetrating trauma individuals who received rFVIIa had non-significantly reduced RBC units over 48 hours compared to no-rFVIIa (5.0±7.4 versus 6.8 ± 6.9; p= 0.11.7)<br>• A retrospective cohort study [7] (n=228) recommend by an expert | No studies were identified. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current. |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
|---|---|---|---|---|
| | reviewer examined rFVIIa compared to no-rFVIIa among massively transfused individuals. The study found reduced RBC units in rFVIIa compared to no-rFVIIa over 6 hours (mean: 35.6±2.6 vs. 25.6±0.7; p=0.001) and 24 hours (mean: 38.6±2.9 vs. 28.0±1.0; p=0.00).<br>• Another retrospective cohort study[6] found no difference between those who received rFVIIa and no-rFVIIa in the number and range of RBC units used (number(range); rFVIIa: 10(6–16) vs no-rFVIIa 10(4–17); p<NS) | | | |
| **Outcome: Acute respiratory distress syndrome (ARDS)**<br>**SOE: Low**<br>**Two RCTs, one comparative observational study**<br>• One blunt trauma RCT identified a significantly lower rate of ARDS in the rFVIIa group compared to the usual care group, while a penetrating trauma RCT and the observational study together suggested a trend in the same direction.<br>Event rates for ARDS were low, | **Assessment: Current**<br>No studies were identified. | No studies were identified. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current. |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
|---|---|---|---|---|
| so the studies were likely underpowered to detect any difference between groups. | | | | |

*Abbreviations:* ARDS=Acute Respiratory Distress Syndrome; RBC=Packed Red Blood Cells; RCT=Randomized Controlled Trial; rFVIIa-Recombinant Factor Seven-A; SOE=Strength of Evidence; TE=Thromboembolic Event
*Studies in italics*= the prior surveillance assessment identified two meta-analyses[3,11]; however upon further review, we discovered that all studies included in these meta-analysis, for these indications, appeared in the original systematic review. Thus, we are not considering these meta-analyses in the determination of currency.

Table 4. Key Question 3b. Use of rFVIIa for Selected Indications in Individuals With/Undergoing Massive Bleeding from Trauma (Brain Trauma) i.e., Traumatic Brain Injury [TBI])

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
|---|---|---|---|---|
| **Outcome: Mortality (15 days)**<br>**SOE: Low**<br>**One RCT, one comparative observational study**<br>• The RCT found no difference between groups in mortality at 15 days, with rates of 11% in each group. The observational study found a reduced mortality with rFVIIa compared to usual care but this was a non-significant finding: 33.3% vs 52.9% in the two groups, respectively.<br>• The findings in both studies are limited by low event rates. | **Assessment: Current**<br>A retrospective cohort study [10] (n=28) found no significant differences between rFVIIa and no-rFVIIa on mortality (50% vs 29%; p=0.22). | Two studies found no difference between rFVIIa and no-rFVIIa groups on mortality.<br>• A retrospective cohort study[15] (n=86) found no significant difference between individuals who received low-dose rFVIIa and matched no-rFVIIa groups on mortality.<br>• A prospective cohort study[17] (n=87) of individuals with TBI and coagulopathy found a non-significant reduction in mortality among those who received low-dose rFVIIa therapy compared to no-rFVIIa. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current. |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
|---|---|---|---|---|
| **Outcome: Thromboembolic events (TEs) (72 hours)**<br>**SOE: Low**<br>**One RCT, one comparative observational study**<br>• The RCT found TE event rates in rFVIIa vs usual care were 16.4% and 5.6% respectively. Half of the events in the rFVIIa group consisted of deep vein thrombosis, all of which were symptomatic. The observational study found TE event rates in rFVIIa vs usual care were 22.2% and 17.6% respectively. One of these events was deep vein thrombosis, which occurred in the usual care group.<br>  • The findings in both studies are limited by low event rates. | **Assessment: Current**<br>Two studies assessed the association between rFVIIa and TEs as compared to no-rFVIIa groups.<br>• *A meta-analysis of 35 total RCTs (one among TBI individuals) reported no difference between rFVIIa and placebo in rates of arterial TEs (3.3% vs 2.8%).*[3]<br>• A retrospective cohort study[10] (n=28) of individuals with TBI undergoing emergent craniotomy reported no TE complications in either the rFVIIa or no-rFVIIa groups. | A retrospective cohort study[15] (n=86) found no occurrence of thromboembolic events in either rFVIIa or matched no-rFVIIa groups. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current. |
| **Outcome: Hematoma volume change**<br>**SOE: Low**<br>**One RCT**<br>• One RCT found a non-significant reduction in hematoma volume change in the rFVIIa group compared to no-rFVIIa group (7.0 mL (SD 12.9) versus 10.4 mL (25.0), respectively). | **Assessment: Current**<br>No studies were identified. | No studies were identified. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current. |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
|---|---|---|---|---|
| **Outcome: RBC Transfusion Requirement**<br>No studies reported on this outcome. | **Assessment: Current***<br>An retrospective study[10] (n=28) among individuals with TBI undergoing emergent craniotomy found a significant reduction of RBC units in individuals receiving rFVIIa versus no-rFVIIa (median(range) of units: preoperative: 0 (0–2) versus 4 (2–8); p= 0.001; intraoperative: 1 (0–2) versus 5 (2–8) ; p=0.002; postoperative: 1 (0–2) versus 3 (2–5); p= 0.002; and total: 4 (1–5) versus 14 (10–17); p= 0.001.) | No studies were identified. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current.<br><br>One study[18] identified in the 2012 surveillance report found a reduction in RBC units among those in the rFVIIa group compared to no rFVIIa, while the original review found no evidence. However, evidence remains insufficient to form a conclusion. |
| **Outcome: ICU length of stay**<br>No studies reported on this outcome. | No studies were identified. | A retrospective cohort study[15] (n=86) found no significant difference between individuals who received low-dose rFVIIa and matched no-rFVIIa individuals on length of ICU stay. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current.<br><br>One study[15] identified in the 2016 surveillance report found no difference between rFVIIa and no-rFVIIa groups on length of ICU stay. However, evidence remains insufficient to form a conclusion. |

*Abbreviations:* ICU=Intensive Care Unit; RCB=Packed Red Blood Cells; RCT=Randomized Controlled Trials; rFVIIa=Recombinant Factor Seven-A; SD=Standard Deviation; SOE=Strength of Evidence; TBI=Traumatic Brain Injury; TE=Thomboembolic Event;
*Studies in italics*= the prior surveillance assessment identified two meta-analyses[3,11]; however upon further review, we discovered that all studies included in these meta-analysis, for these indications, appeared in the original systematic review. Thus, we are not considering these meta-analyses in the determination of currency.

Table 5. Key Question 4a: Use of rFVIIa for Selected Indications in Individuals With/Undergoing Liver Transplantation

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
|---|---|---|---|---|
| **Outcomes: Mortality**<br>**SOE: Low**<br>**Three RCTs**<br>• The RCTs found no difference in mortality rates between groups, although the studies were not sufficiently powered for this outcome. | **Assessment: Current**<br>*A meta-analysis of four RCTs[11] (two among liver transplantation individuals and two among liver resection individuals) recommended by an expert reviewer found no difference in mortality between rFVIIa and placebo groups (OR=0.96, 95% CI: 0.35, 2.62).* | An retrospective cohort study[16] (n=183) compared the use of rFVIIa preemptively or intraoperatively to a matched no-rFVIIa group and found that individuals who received rFVIIa preemptively had similar mortality rates as the no-rFVIIa group, but individuals who received rFVIIa intraoperatively had increased mortality rates at 30 days and one year. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current.<br><br>An observational study[16] identified in the 2016 surveillance report indicates that mortality rates are similar among those who received rFVIIa pre-emptively vs. no rFVIIa, which is consistent with the original systematic review's conclusions on prophylactic use of rFVIIa. The study also indicates that mortality is higher among those who receive rFVIIa intraoperatively vs. no rFVIIa. Intraoperative rFVIIa use was not discussed in the original systematic review. |
| **Outcomes: Thromboembolic events**<br>**SOE: Low**<br>**Three RCTs, one comparative observational study**<br>• The RCTs found no | **Assessment: Current**<br>No studies were identified. | No studies were identified. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current. |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
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| differences in TEs between groups. The observational study only reported one thromboembolic event - thrombosis of the hepatic artery in a patient who received rFVIIa. | | | | |
| **Outcomes: Units of RBCs transfused in 24-hour post-operative period**<br>**SOE: Low**<br>**Three RCTs, one comparative observational study**<br>One RCT found a significant reduction in RBC units with rFVIIa, one RCT found a non-significant reduction in RBC units with rFVIIa, and one RCT found no difference between rFVIIa versus usual care. The observational study found significantly lower RBC transfusion requirements with rFVIIa. | **Assessment: Current***<br>*A meta-analysis of four RCTs[11] (two among liver transplantation individuals and two among liver resection individuals) recommended by an expert reviewer found no difference in units of RBCs between rFVIIa and placebo (Mean difference: 0.32, 95% CI: -0.08, 0.72).* | An retrospective cohort study[16] (n=183) compared the use of rFVIIa preemptively or intraoperatively to a matched no-rFVIIa group and found that individuals who received rFVIIa intraoperatively required more blood products than individuals receiving rFVIIa preemptively or the no-rFVIIa group. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current.<br><br>An observational study[16] identified in the 2016 surveillance report found increased blood products among groups receiving rFVIIa intraoperatively versus rFVIIa preemptively or the no-rFVIIa group. Intraoperative rFVIIa use was not discussed in the original systematic review. |
| **Outcomes: Operating Room Time**<br>**SOE: Low**<br>**One RCT, one comparative observational study**<br>One RCT identified a significant difference between groups in operating room time, with transplantation taking over 200 | **Assessment: Current**<br>No studies were identified. | No studies were identified. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current. |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
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| minutes less in the rFVIIa group compared to placebo. None of the other studies identified a significant difference between groups | | | | |
| **Outcomes: ICU length of stay**<br>**SOE: Low**<br>**Three RCTs**<br>Three RCTs found no difference between groups in ICU length of stay. | **Assessment: Current**<br>No studies were identified. | An retrospective cohort study[16] (n=183) compared the use of rFVIIa preemptively or intraoperatively to a matched no-rFVIIa group and found that individuals who received rFVIIa intraoperatively had longer ICU stays than those receiving rFVIIa preemptively or the no-rFVIIa group. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current.<br><br>An observational study[16] found that those who received rFVIIa intraoperatively had longer ICU stays than those receiving rFVIIa preemptively and the no-rFVIIa group. Intraoperative use of rFVIIa was not discussed in the original systematic review. |

*Abbreviations:* CI=Confidence Interval; ICU=Intensive Care Unit; RBC=Packed Red Blood Cells; RCT=Randomized Controlled Trial; rFVIIa=Recombinant Factor Seven-A; SOE=Strength of Evidence; TE=Thromboembolic Event
*Studies in italics*= the prior surveillance assessment identified two meta-analyses[3,11]; however upon further review, we discovered that all studies included in these meta-analysis, for these indications, appeared in the original systematic review. Thus, we are not considering these meta-analyses in the determination of currency.
*Indicates the assessment of currency was changed from "possibly out of date" to "current" in the current review due to the removal of the two meta-analyses[3,11] whose results were previously included in the original systematic review.

Table 6. Key Question 4b.i. Use of rFVIIa for Selected Indications in Individuals With/Undergoing Cardiac Surgery (Adult Cardiac Surgery)

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
|---|---|---|---|---|

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
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| **Outcomes: Mortality (in-hospital)**<br>**SOE: Low**<br>**Two RCTs, four comparative observational studies, four meta-analyses**<br>Meta-analysis of good-quality RCTs and observational studies found no difference in mortality between rFVIIa and usual care (risk difference 0.007; 95% CI -0.049 to 0.063) | **Assessment: Current**<br>No studies were identified. | No studies were identified. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current. |
| **Outcomes: Thromboembolic events**<br>**SOE: Moderate**<br>**Two RCTs, four comparative observational studies, four meta-analyses**<br>Meta-analysis of RCTs and good quality observational studies identified a higher rate of thromboembolic events in the rFVIIa group compared to the no-rFVIIa group (risk difference 0.053; 95% CI 0.01 to 0.096) | **Assessment: Current**<br>*A meta-analysis[3] of 35 RCTs (two among adult and one among pediatric cardiac surgery individuals) found no significant effect of rFVIIa on arterial TE event rates compared to placebo (odds ratio=1.59, 95% CI: 0.47, 5.34; p= 0.45).* | No studiewere identified. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current. |
| **Outcomes: Units of RBCs transfused in 24 hours**<br>**SOE: Low**<br>**One RCT, three comparative observational studies**<br>A RCT and a good quality observational study found a non-significant and significant difference between groups that favored rFVIIa use over no- | **Assessment: Current**<br>No studies were identified. | No studies were identified. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current. |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
|---|---|---|---|---|
| rFVIIa groups, respectively (p values 0.11 and <0.001). One additional observational study found no difference between groups, and another found a significant effect against the rFVIIa group (i.e., increased transfusions with treatment). | | | | |
| **Outcomes: ICU length of stay**<br>**SOE: Low**<br>**One RCT, four comparative observational studies**<br>One RCT found no significant difference between groups in ICU length of stay. Findings among observational studies were inconsistent: one cohort study found a significantly longer ICU length of stay for rFVIIa individuals but two others had significant and non-significant findings in the opposite direction, respectively. A fourth cohort study found no difference between groups. | **Assessment: Current**<br>No studies were identified. | No studies were identified. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current. |
| **Outcome: Operating room time**<br>No studies reported on this outcome. | **Assessment: Current**<br>A retrospective chart review[12] (n=24) recommended by an expert reviewer reported lesser median operating room time for rFVIIa group versus reoperation for refractory bleeding after surgery group, however, the data were not reported. | No studies were identified. | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current. |

*Abbreviations:* CI=Confidence Interval; ICU=Intensive Care Unit; RBC=Packed Red Blood Cells; RCT=Randomized Controlled Trial; rFVIIa=Recombinant Factor Seven-A; SOE=Strength of Evidence; TE=Thromboembolic Event
*Studies in italics*= the prior surveillance assessment identified two meta-analyses[3,11]; however upon further review, we discovered that all studies included in these meta-analysis, for these indications, appeared in the original systematic review. Thus, we are not considering these meta-analyses in the determination of currency.

Table 7.Key Question 4b.ii. Use of rFVIIa for Selected Indications in Patient With/Undergoing Cardiac Surgery (Pediatric Cardiac Surgery)

| **Conclusions From Original Systematic Review (May 2010) Link to report** | **Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report** | **Literature Analysis (December 2015)** | **Expert Opinion** | **Surveillance Assessment** |
|---|---|---|---|---|
| **Outcomes: Mortality (in-hospital)**<br>**SOE: Insufficient**<br>No studies were identified. | **Assessment: Current**<br>A retrospective matched case-control study [20] (n=75) found no significant difference between individuals receiving rFVIIa and a matched no-rFVIIa group on mortality. | A retrospective matched case-control study [14] (n=135) of individuals who received rFVIIa (during or after cardiac surgery) and matched no-rFVIIa group found no significant differences in mortality rates (16% vs 9.5%, p=.208). | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current.<br><br>While the original systematic review found no studies examining this outcome, the 2012 and 2016 surveillance reports each identified a retrospective matched case-control study[8,14] indicating there are no differences between rFVIIa and no-rFVIIa in mortality. Evidence remains insufficient. |
| **Outcomes: Thromboembolic events**<br>**SOE: Insufficient**<br>**One RCT**<br>One RCT identified no thromboembolic events in either rFVIIa or usual care groups. | **Assessment: Current**<br>A retrospective matched case-control [20] (n=75) found no significant differences between individuals receiving rFVIIa and a matched no-rFVIIa group on rate of TE (8% versus 4%; p=NR). | A retrospective matched case-control study [14] (n=135) of individuals who received rFVIIa (during or after cardiac surgery) and matched no-rFVIIa group found no significant differences in the rate of thrombosis (20% vs 28%, p=.540). | One expert felt the original conclusion was still current, and the other did not comment on currency. | Conclusions are likely current.<br><br>While the original systematic review reported insufficient evidence for this outcome, the 2012 and 2016 surveillance report each identified |

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
|---|---|---|---|---|
| | | | | one retrospective matched case-control study[8,14] indicating there are no differences between rFVIIa and no-rFVIIa in rates of TEs. |
| **Outcomes: Units of Whole Blood/RBC transfusion**<br>**SOE: Insufficient**<br>**One RCT**<br>One RCT found a non-significant decrease in transfusion requirements for RBCs and/or whole blood in the rFVIIa group compared to no-rFVIIa groups. | **Assessment: Current**<br>A retrospective matched case-control [20] (n=75) found no significant differences between individuals receiving rFVIIa and a matched no-rFVIIa group on RBC transfusion requirements (93.2 mL/kg versus 108.3 mL/kg; p = 0.225). | No studies were identified. | One expert felt the original conclusion was still current, and the other did not comment on currency | Conclusions are likely current. |
| **Outcomes: Time to chest closure**<br>**SOE: Insufficient**<br>**One RCT**<br>One RCT found that rFVIIa individuals had a longer time to chest closure than did no-rFVIIa groups (98.8 minutes (SE 27.3) versus 58.3 minutes (SE 29.2), p=0.026). | **Assessment: Current**<br>No studies were identified. | No studies were identified. | One expert felt the original conclusion was still current, and the other did not comment on currency | Conclusions are likely current. |

*Abbreviations:* NR=Not Reported; RBC=Packed Red Blood Cells; RCT=Randomized Controlled Trial; rFVIIa=Recombinant Factor Seven-A; SE=Standard Error; SOE=Strength of Evidence

Table 8. Key Question 4c. Use of rFVIIa for Selected Indications in Patient With/Undergoing Prostatectomy

| Conclusions From Original Systematic Review (May 2010) Link to report | Findings and Assessment from Most Recent Surveillance Assessment (February 2012) Link to report | Literature Analysis (December 2015) | Expert Opinion | Surveillance Assessment |
|---|---|---|---|---|
| **Outcomes: Mortality (10 day)**<br>**SOE: Insufficient**<br>**One RCT**<br>One RCT reported no deaths in either rFVIIa or no-rFVIIa groups. | **Assessment: Current**<br>No studies were identified. | No studies were identified. | One expert felt the original conclusion was still current, and the other did not comment on the currency. | Conclusions are likely current. |
| **Outcomes: Thromboembolic events**<br>**SOE: Insufficient**<br>**One RCT**<br>One RCT reported a single TE (myocardial infarction) in the 20 µg/kg dose of rFVIIa group. | **Assessment: Current**<br>No studies were identified. | No studies were identified. | One expert felt the original conclusion was still current, but noted that prostatectomy is now associated with lower morbidity due to the use of laparoscopic and robotic technology. The other expert did not comment on currency. | Conclusions are likely current. |
| **Outcomes: Units of RBCs transfused**<br>**SOE: Insufficient**<br>**One RCT**<br>One RCT found significantly reduced RBC transfusion requirements in the rFVIIa group compared to usual care. | **Assessment: Current**<br>No studies were identified. | No studies were identified. | One expert felt the original conclusion was still current, and the other did not comment on currency | Conclusions are likely current. |
| **Outcomes: Operative Room time**<br>**SOE: Insufficient**<br>**One RCT**<br>One RCT found significantly reduced operating room time in the rFVIIa group compared to usual care | **Assessment: Current**<br>No studies were identified. | No studies were identified. | One expert felt the original conclusion was still current, and the other did not comment on currency | Conclusions are likely current. |

*Abbreviations:* RBC=Packed Red Blood Cells; RCT=Randomized Controlled Trial; rFVIIa=Recombinant Factor Seven-A; SOE=Strength of Evidence; TE=Thromboembolic Event

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